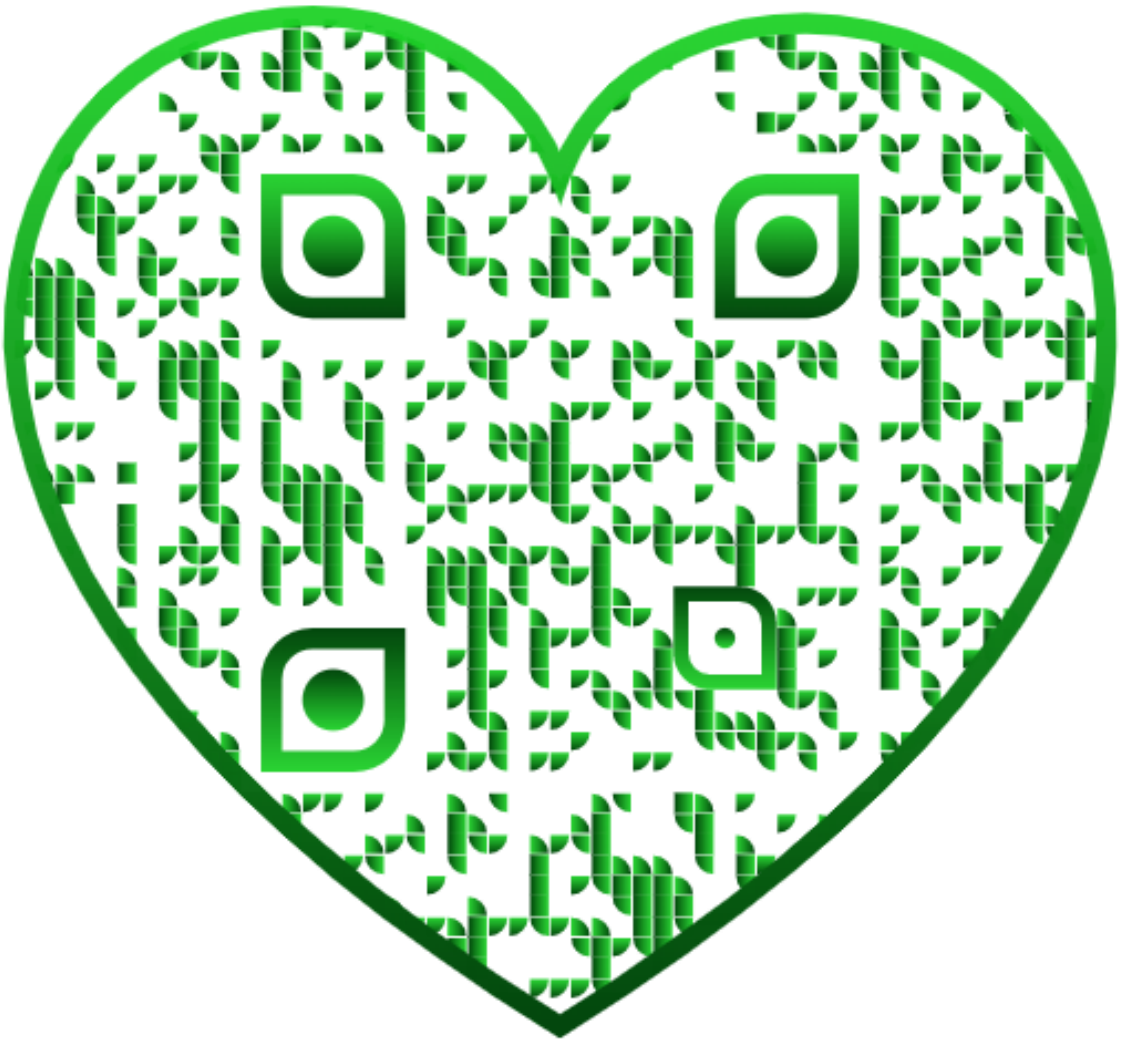
Terpenoids

Topic outline

- Introduction
- The Isoprene rule and biosynthesis
- Classification of terpenoids
- Properties and isolation of terpenoids
- Significance of terpenoids



I. Introduction

- Terpnoids and steroids constitute the largest known group of plant secondary metabolites.
- Descriptions: Terpenes and Terpenoids
  - **Terpene** refers to any of a class of hydrocarbons occurring widely in plants and animals
  - The term is often extended to the **terpenoids**, which are **oxygenated derivatives** of these hydrocarbons.

Introduction cont.

– **Terpenes** and **terpenoids** are

- ✓ The most important constituents in essential oils
- ✓ Built from C5 isoprene units or
- ✓ Repeating isoprene units

Introduction cont.

- Occurrence:
  - The vast majority of terpenes are specific to the vegetable kingdom, but they also occur in animals.
  - Although more commonly associated with coniferous species, terpenes have been detected in other plant phyla, including angiosperms.

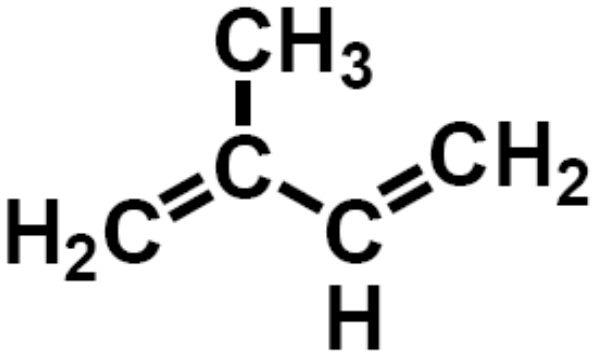
Introduction cont.

- Terpenoids are found in **all parts** of higher plants and occur in mosses, liverworts, algae and lichens.
- Terpenoids of insect and microbial origin have also been found.

2. The Isoprene rule

- **Isoprene** is a five carbon unit, chemically known as
  - 2-methyl-1, 3-butadiene
- An **isoprene unit** is the carbon skeleton of isoprene (ignoring the double bonds)

The Isoprene rule cont.



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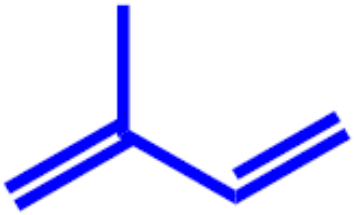
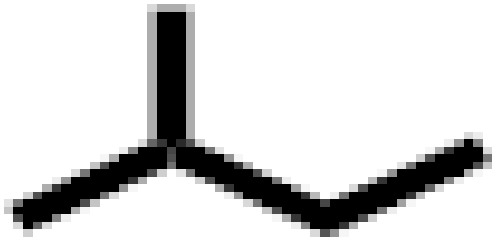


Isoprene
(2-methyl-1, 3-butadiene)



Isoprene unit

The Isoprene rule cont.

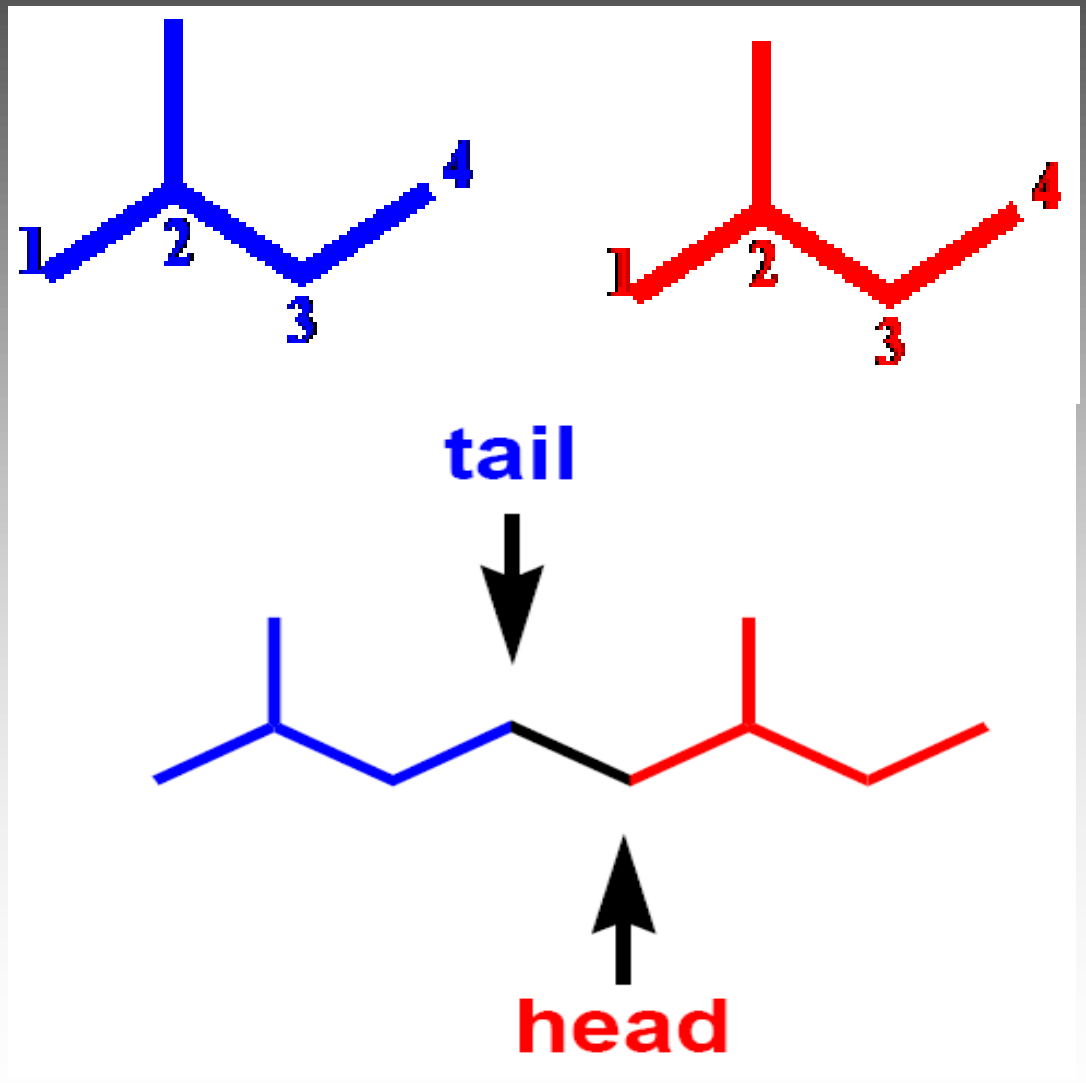
2.1 Chemistry and structure of terpenoids

- The isoprene unit can build upon itself in various ways
  - All terpenes my be considered as compounds formed by the assembly of a whole number of isoprene unit
  - This is best explained by the isoprene rule

The Isoprene rule cont.

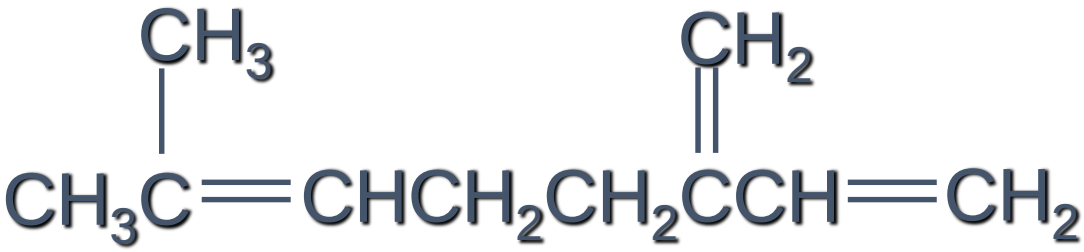
- **The Isoprene Rule**
  - **Isoprene rule** states that the terpenoid molecules are constructed from two or more isoprene unit
  - **Special isoprene rule** states that the terpenoid molecules are constructed of two or more isoprene units joined in a 'head to tail' fashion.
    - ✓Carbon 1 is called the 'head' and carbon 4 is the 'tail'.

The Isoprene rule cont.



The Isoprene rule cont.

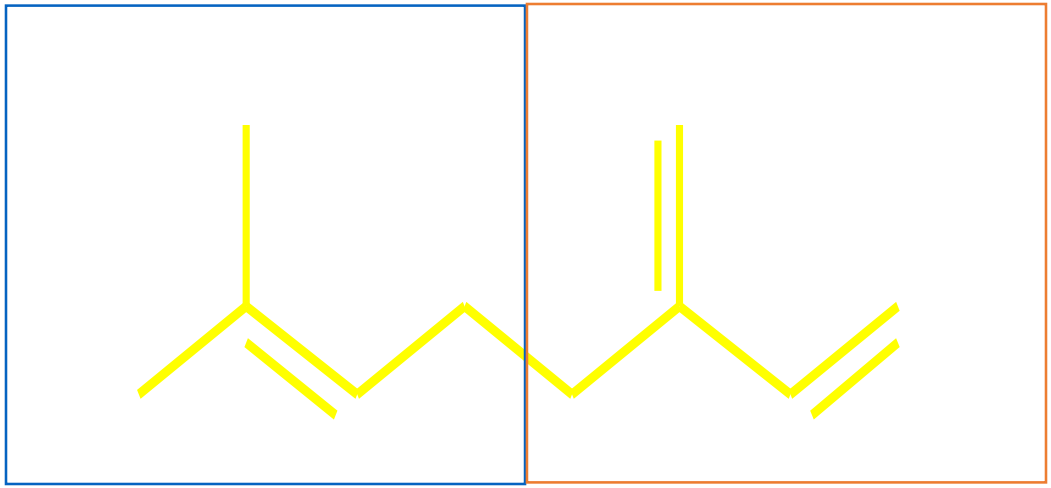
- *For example, Myrcene is a simple 10-carbon-containing terpenoid formed from the head-to-tail union of two isoprene units.*



or

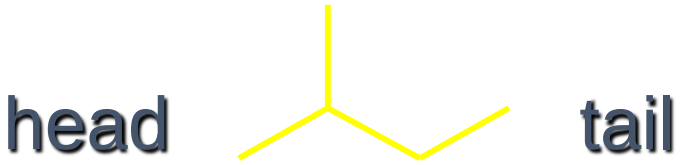
The Isoprene rule cont.

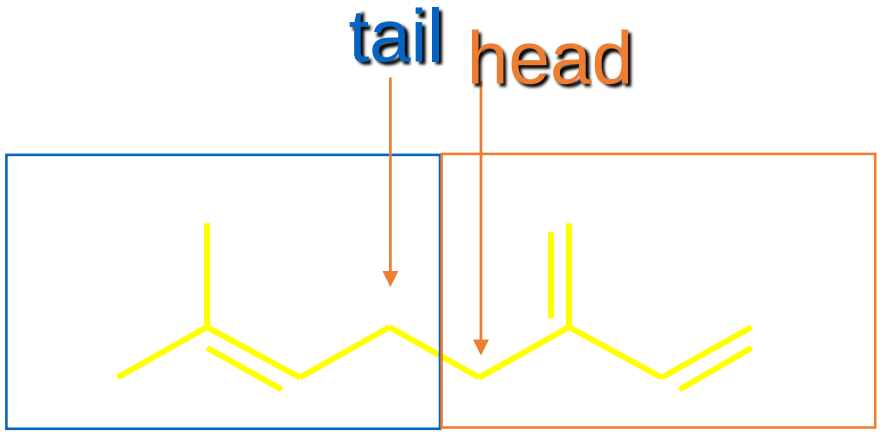
Myrcene contains two isoprene units.



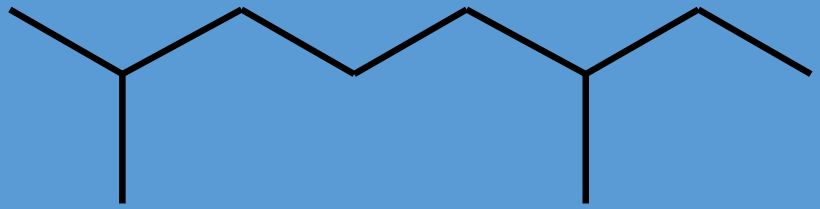
The Isoprene rule cont.

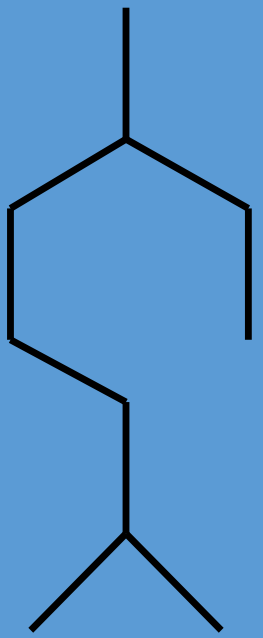
- The isoprene units of myrcene are joined "head-to-tail."

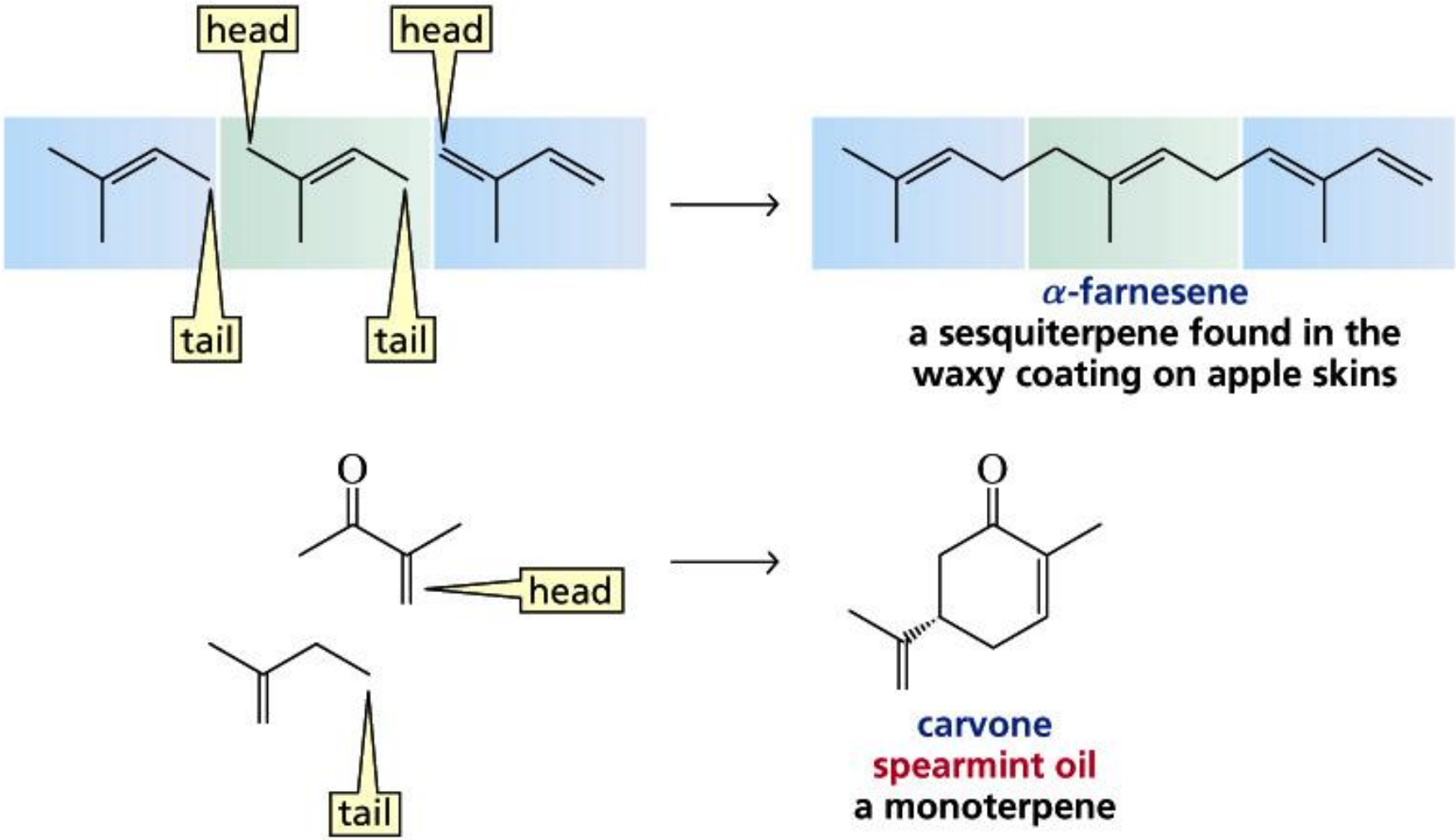




Common Carbon Backbone






head
head
tail
tail
α-farnesene
a sesquiterpene found in the waxy coating on apple skins
O
head
tail
O
carvone
spearmint oil
a monoterpene

The Isoprene rule cont.

- **Note:**
  - ✓ The isoprene rule can only be used
    - ➢ as guiding principle and not as a fixed rule.
  - ✓ For example:
    - ➢ carotenoids are joined tail to tail at their central and
    - ➢ there are also some terpenoids whose carbon content is not a multiple of five.

The Isoprene rule cont.

✓In each group of terpenoids, a unique precursor leads to the different known constituents by a succession of classic reactions:

- cyclization,
- functionalization, or
- rearrangements

✓Steroids are examples of modified triterpenoids

The Isoprene rule cont.

- 2.2 Classification of terpenoids
- Most natural terpenoid hydrocarbons have the general formula $(C_5H_8)_n$.
- They can be classified on the basis of
  - value of n (number of isoprene units) or
  - number of carbon atoms present in the structure.

Classification cont.

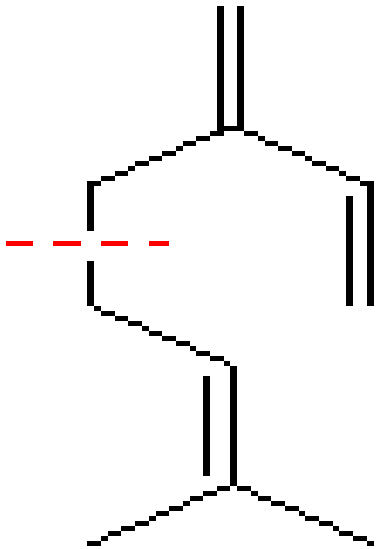
S.No.	Number of carbon atoms	Value of n	Class
1	5	1	Hemiterpenes(C_5H_8)
2	10	2	Monoterpenoids($C_{10}H_{16}$)
3	15	3	Sesquiterpenoinds($C_{15}H_{24}$)
4	20	4	Diterpenoids($C_{20}H_{32}$)
5	25	5	Sesterpenoids($C_{25}H_{40}$)
6	30	6	Triterpenoids($C_{30}H_{48}$)
7	40	8	Tetratepenoids ($C_{40}H_{64}$)
8	>40	>8	Polytepenoids (>$C_{40}H_{64}$) or Higher terpenoids

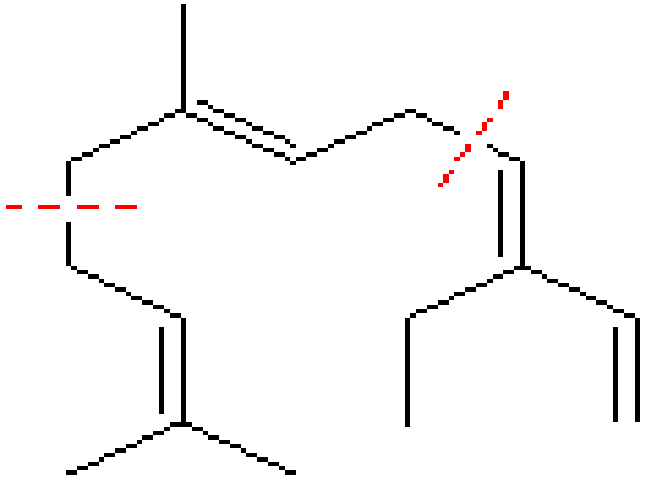
Classification cont.

- Each class can be further subdivided into subclasses according to the number of rings present in the structure.
  - ✓ Acyclic: *open structure*
  - ✓ Cyclic: *ring structure.*
    - Monocyclic: *one ring in the structure.*
    - Bicyclic: *two rings in the structure.*
    - Tricyclic: *three rings in the structure.*
    - Tetracyclic: *four rings in the structure.*

The Isoprene rule cont.

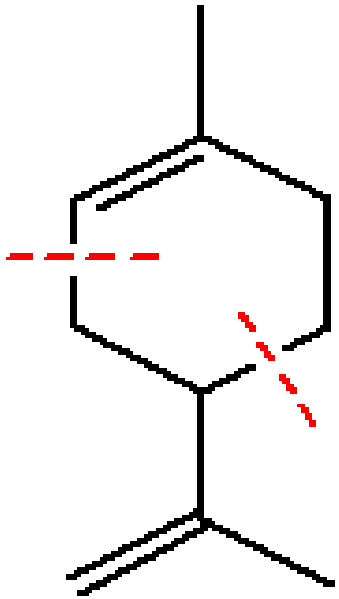
- Recognition of the isoprene unit as a component of the structure of terpenes has been a great aid in elucidating their structures.



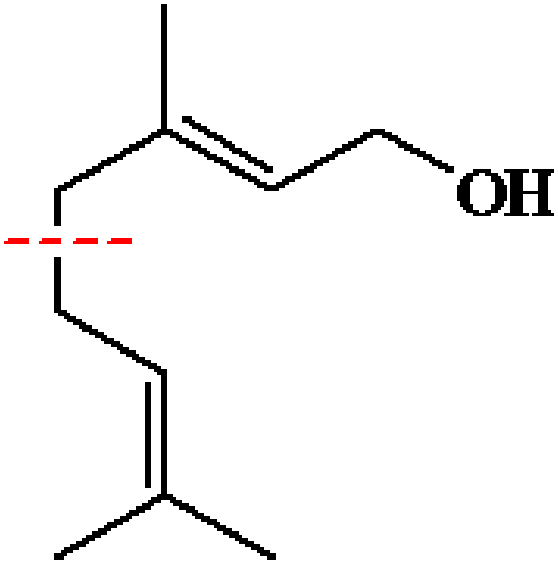


The Isoprene rule cont.

- Many terpenes also have isoprene units linked in rings, and others (terpenoids) contain oxygen.



Limonene

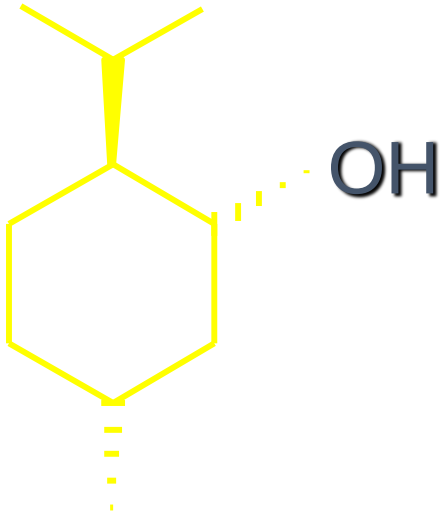


Geraniol

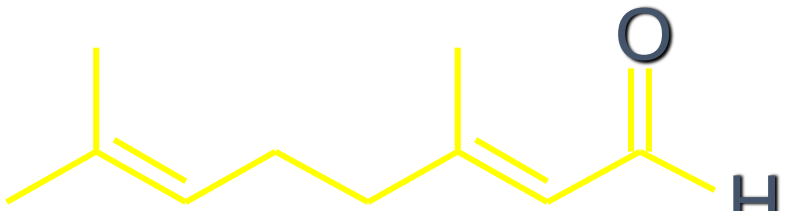
The Isoprene rule cont.

Representative Monoterpenes (2 Isoprene unit)

α-Phellandrene
(eucalyptus)



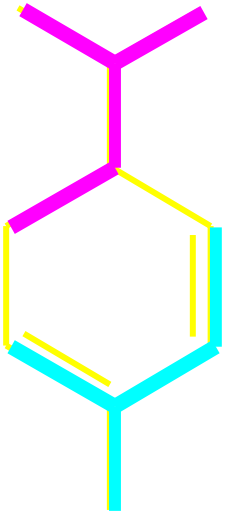
Menthol
(peppermint)



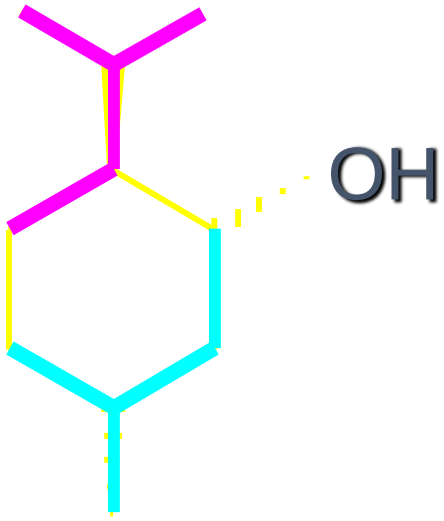
Citral
(lemon grass)

The Isoprene rule cont.

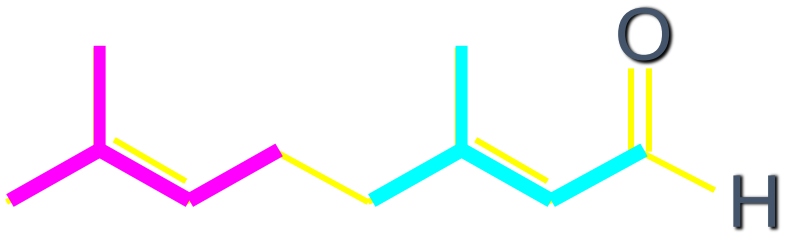
Representative Monoterpenes (2 Isoprene unit)



α-Phellandrene
(eucalyptus)



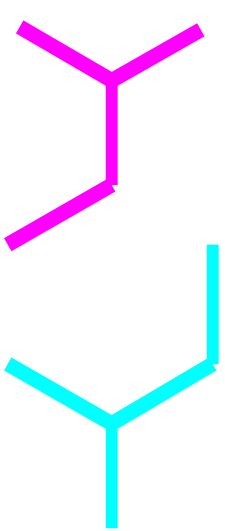
Menthol
(peppermint)



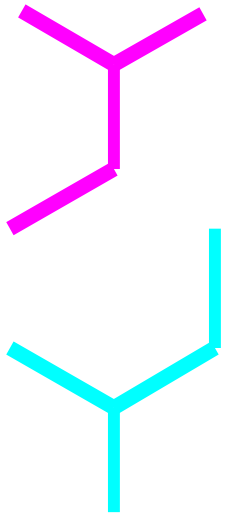
Citral
(lemon grass)

The Isoprene rule cont.

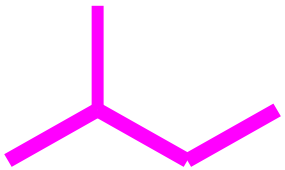
Representative Monoterpenes (2 Isoprene unit)

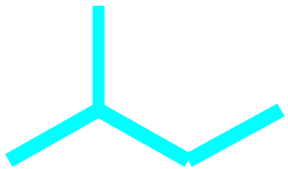


a-Phellandrene
(eucalyptus)



Menthol
(peppermint)

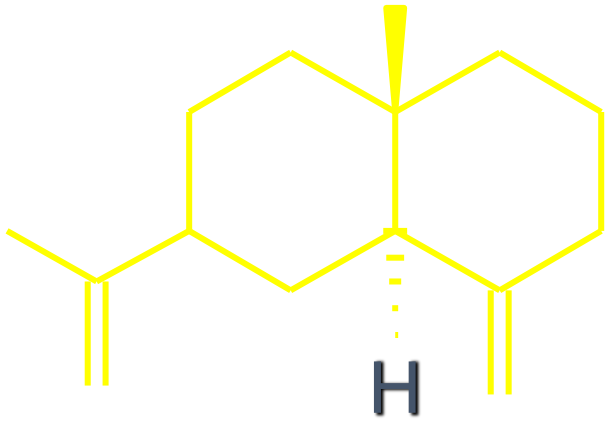




Citral
(lemon grass)

The Isoprene rule cont.

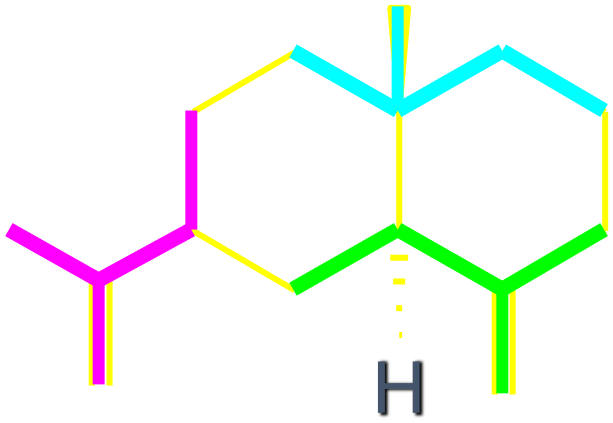
Representative Sesquiterpenes (3 Isoprene unit)



α-Selinene
(celery)

The Isoprene rule cont.

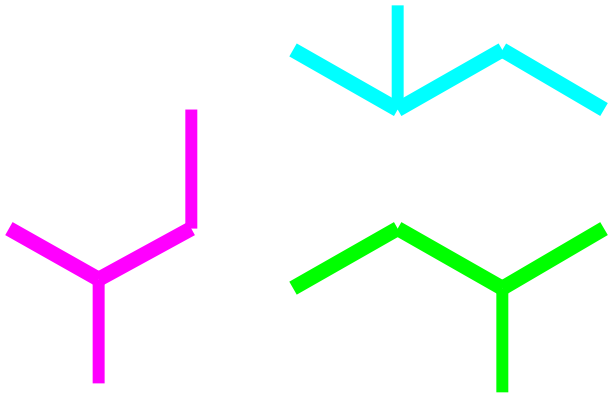
Representative Sesquiterpenes (3 Isoprene unit)



α-Selinene
(celery)

The Isoprene rule cont.

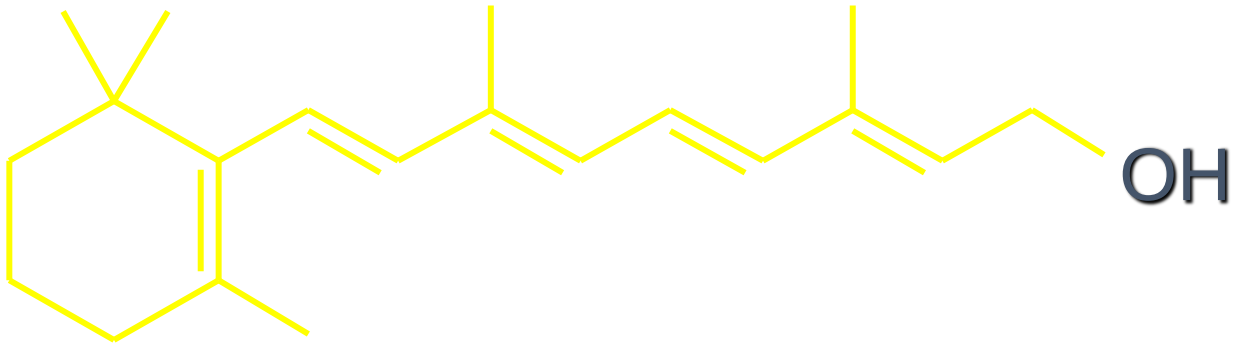
Representative Sesquiterpenes (3 Isoprene unit)



α-Selinene
(celery)

The Isoprene rule cont.

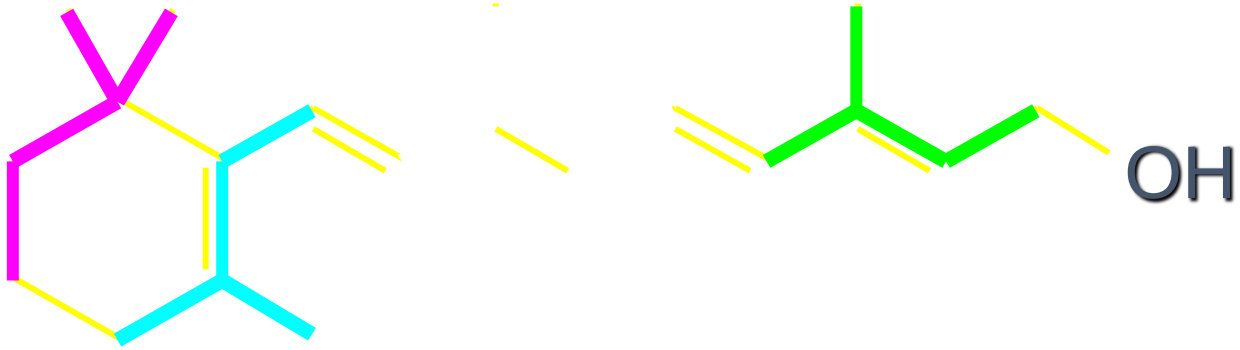
Representative Diterpenes(4 Isoprene unit)



Vitamin A

The Isoprene rule cont.

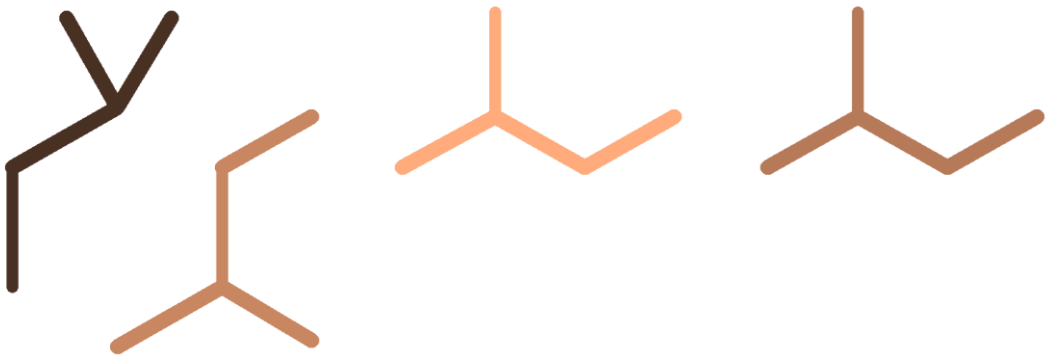
Representative Diterpenes(4 Isoprene unit)



Vitamin A

The Isoprene rule cont.

Representative Diterpenes(4 Isoprene unit)



Vitamin A

The Isoprene rule cont.

- 2.2 Biosynthesis of terpenoids
- 2.2.1 Biosynthesis of the biological isoprene unit: Isopentenyl pyrophosphate

❖ Isoprene

– is produced naturally but is not involved in the formation of terpenoid compounds (as was thought previously), and

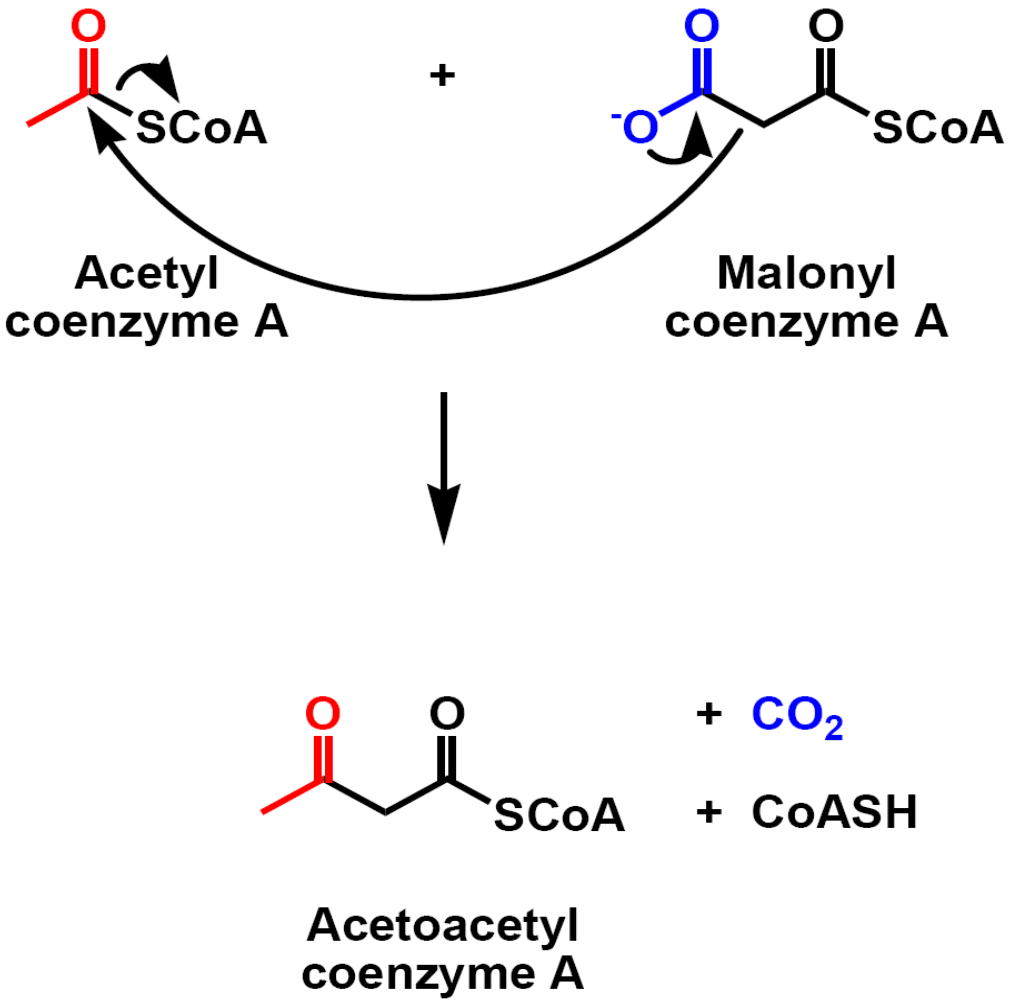
Biosynthesis biological isoprene unit cont.

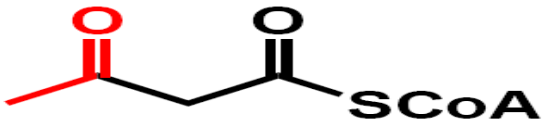
—the biochemically active isoprene units were identified as the diphosphate (pyrophosphate) esters:

- ✓ **dimethylallyl diphosphate (DMAPP)** and
- ✓ **isopentenyl diphosphate (IPP).**

Biosynthesis biological isoprene unit cont.

- Isoprenoid compounds are synthesized from **acetate!!**
- The biological isoprene unit is biosynthesized as follows

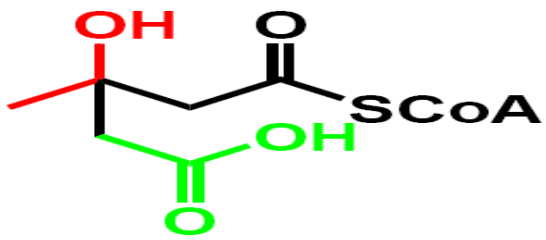




Acetoacetyl coenzyme A

+

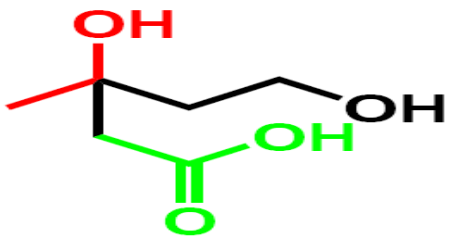
Acetyl coenzyme A

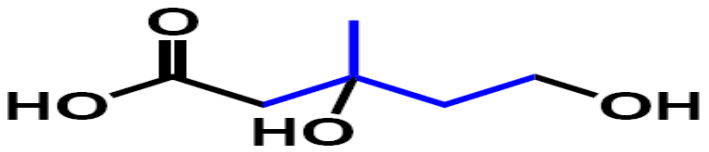


+ CoASH

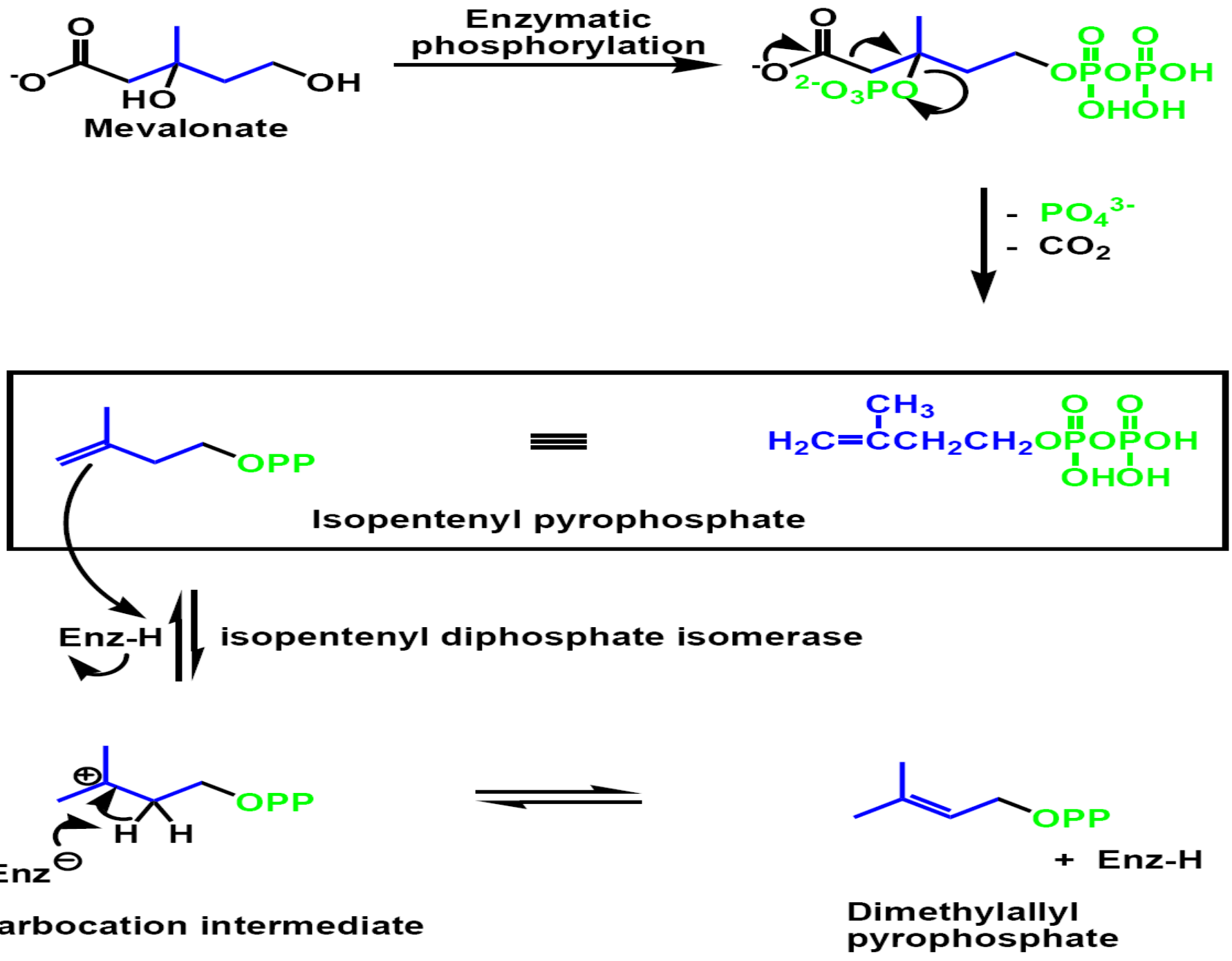
3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA)

Enzymatic reduction





Mevalonic acid

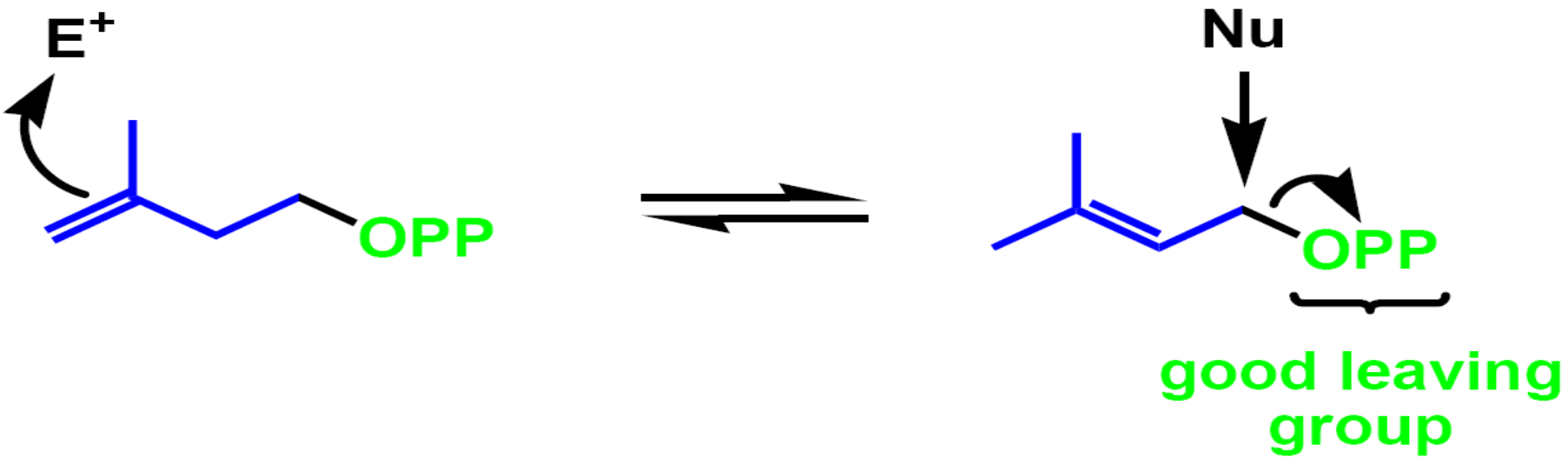

Mevalonate
Enzymatic phosphorylation
- PO_4^{3-}
- CO_2
OPP
Isopentenyl pyrophosphate
Enz-H
isopentenyl diphosphate isomerase
Enz
Carbocation intermediate
OPP
+ Enz-H
Dimethylallyl pyrophosphate

The biological isoprene unit cont.

IPP is isomerized by isopentenyl isomerase to **DMAPP**.

Isopentenyl pyrophosphate (reactive C=C)

Dimethylallyl pyrophosphate (reactive allylic C)

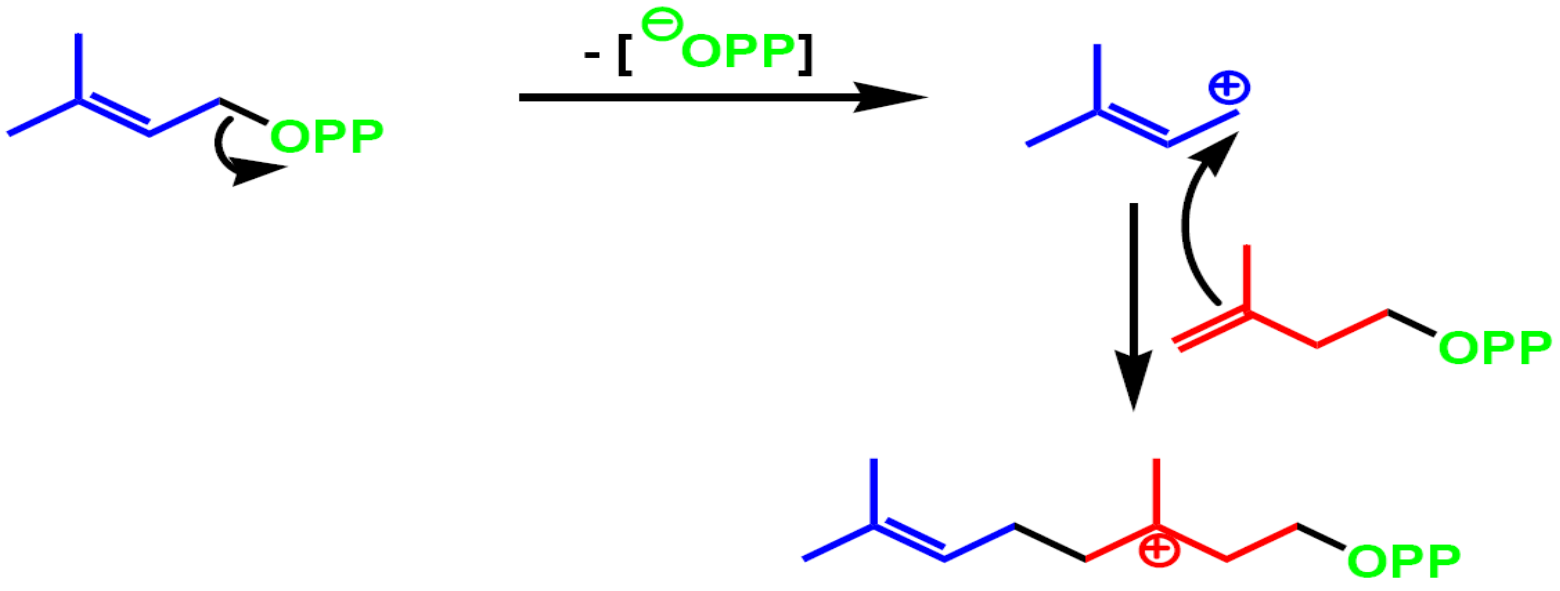


The biological isoprene unit cont.

- IPP and DMAPP are
  - structurally similar but have different chemical reactivity
  - DMAPP
    - ✓ has a leaving group (pyrophosphate) at an allylic carbon;
    - ✓ is reactive toward nucleophilic substitution at this position.

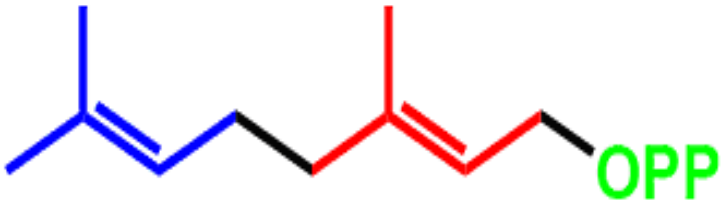
The biological isoprene unit cont.

- The precursor for the chief classes of terpenes
  - ➢ are formed by reactions catalyzed by enzymes, and
  - ➢ are phosphoric esters of C-5 alcohols formed by the sequential addition of IPP on to a starter molecule DMAPP
- The process involves typical carbocation reactions
  - ✓ The C-C bond formation
  - ✓ The key process involves the double bond of IPP acting as a nucleophile toward the allylic carbon of DMAPP.



a. geranylpyrophosphate (GPP),

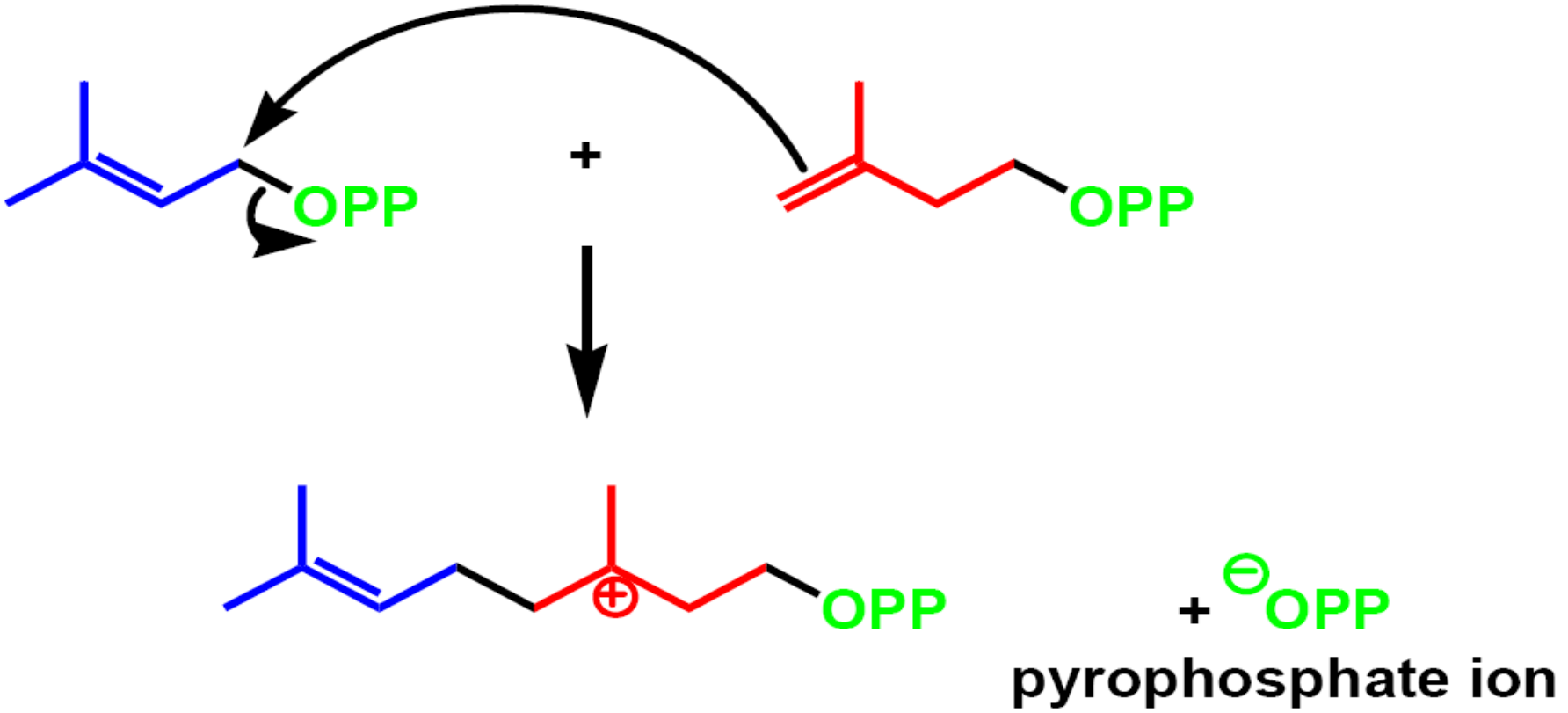
DMAPP + IPP = GPP



✓precursor of C10 monoterpenes

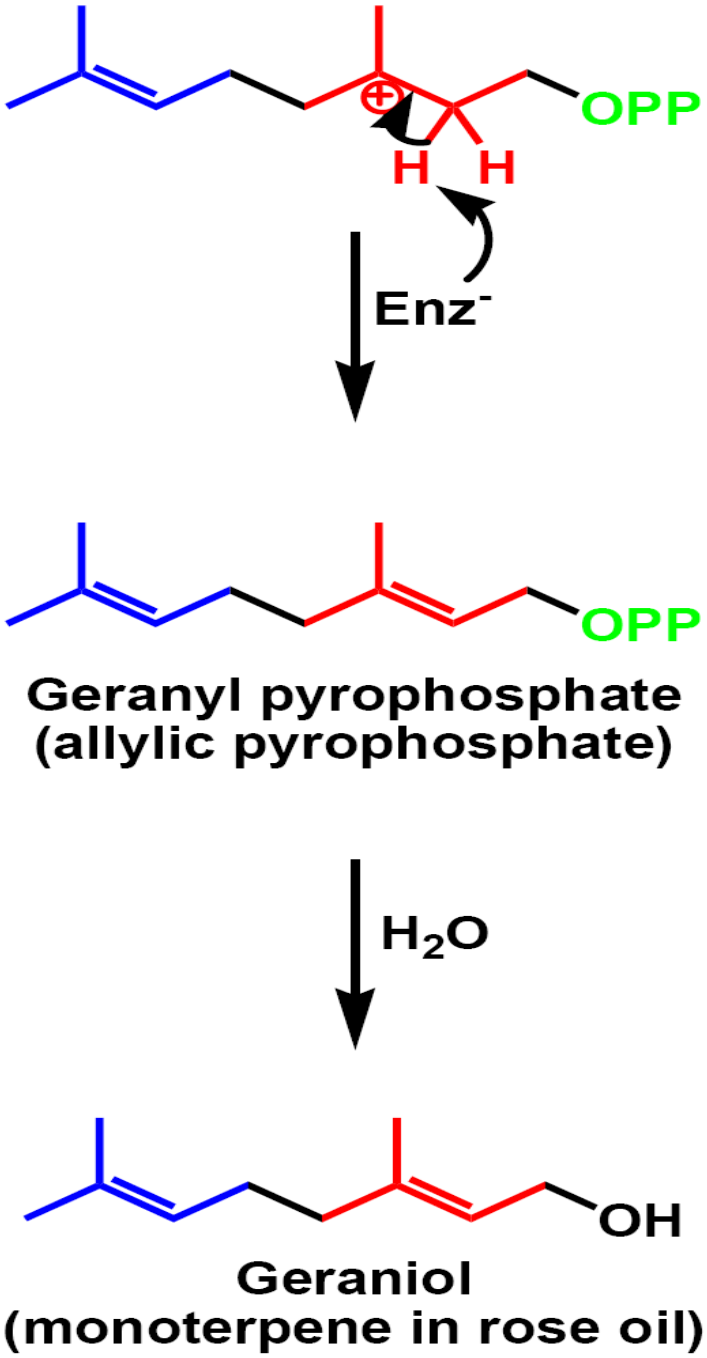
GPP cont.

✓A unit of IPP and a unit of DMAPP are combined together head to tail by dimethylallyl transferase to form GPP.

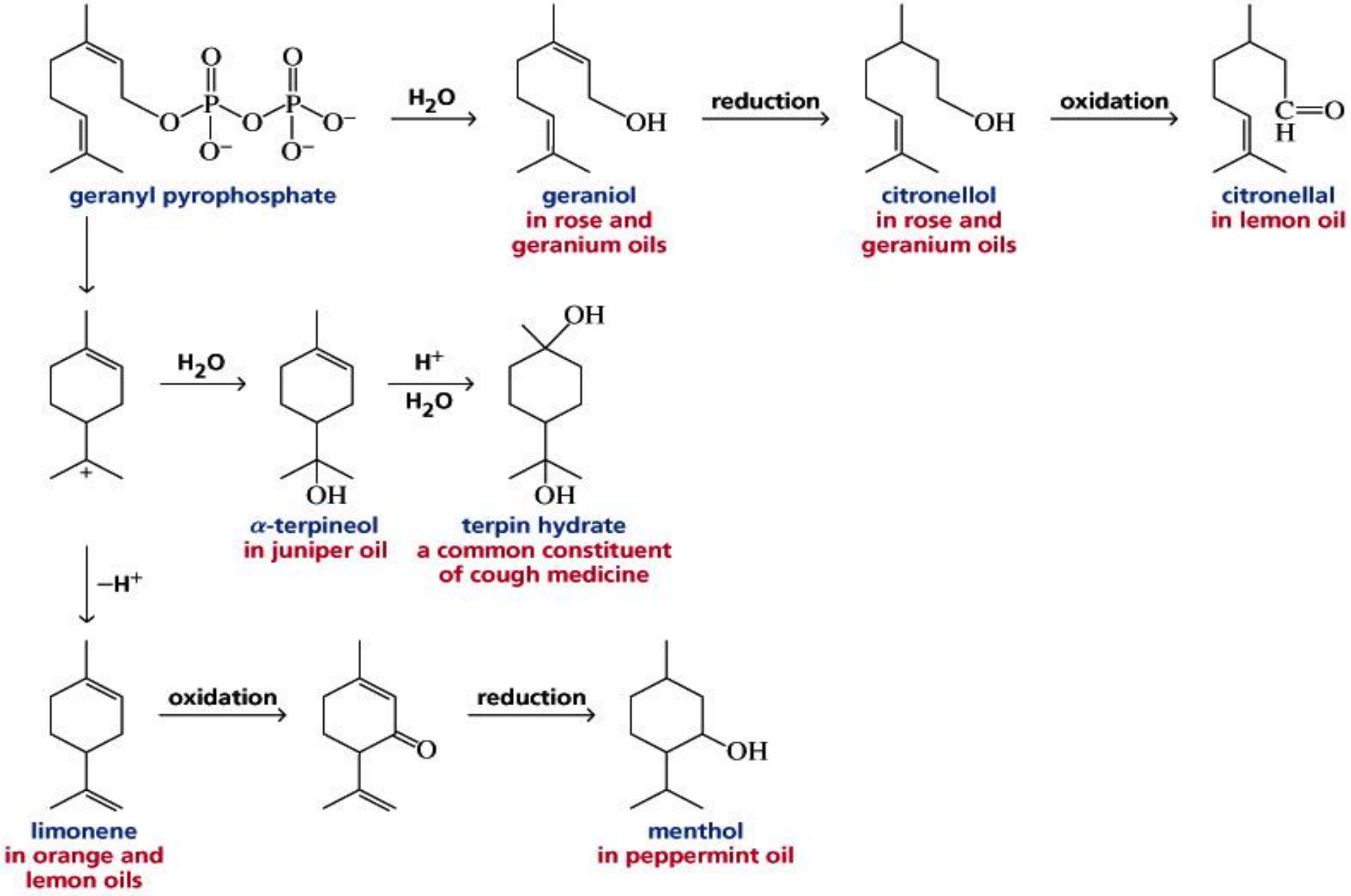


GPP cont.

- 10-C intermediate undergoes typical carbocation reactions



✓GPP ⇒ precursor of C10 monoterpenes



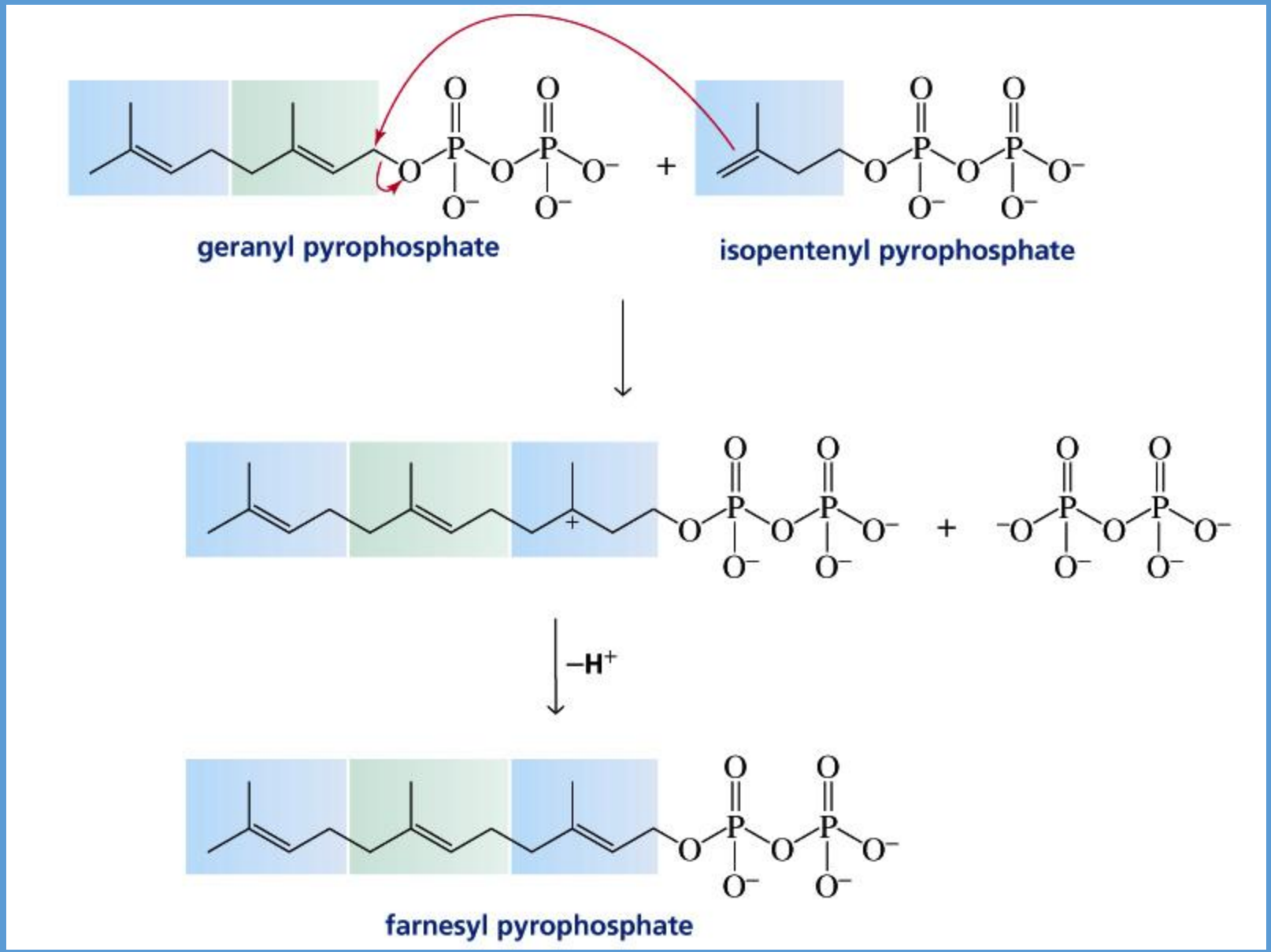
Biosynthesis of terpenoids cont.

b. farnesylpyrophosphate (FPP)

GPP + IPP = FPP

✓ precursor of C_{15} sesquiterpenes

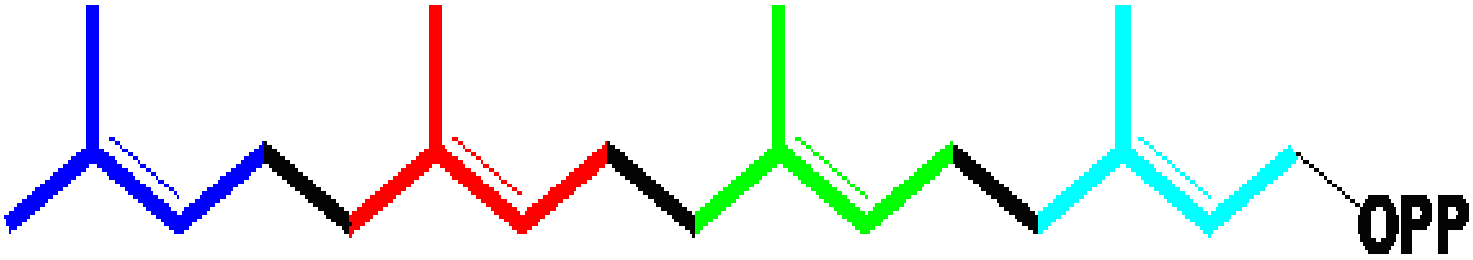
FPP cont.


geranyl pyrophosphate
isopentenyl pyrophosphate
–H+
farnesyl pyrophosphate

Biosynthesis of terpenoids cont.

- c. geranyl geranylpyrophosphate (GGPP)

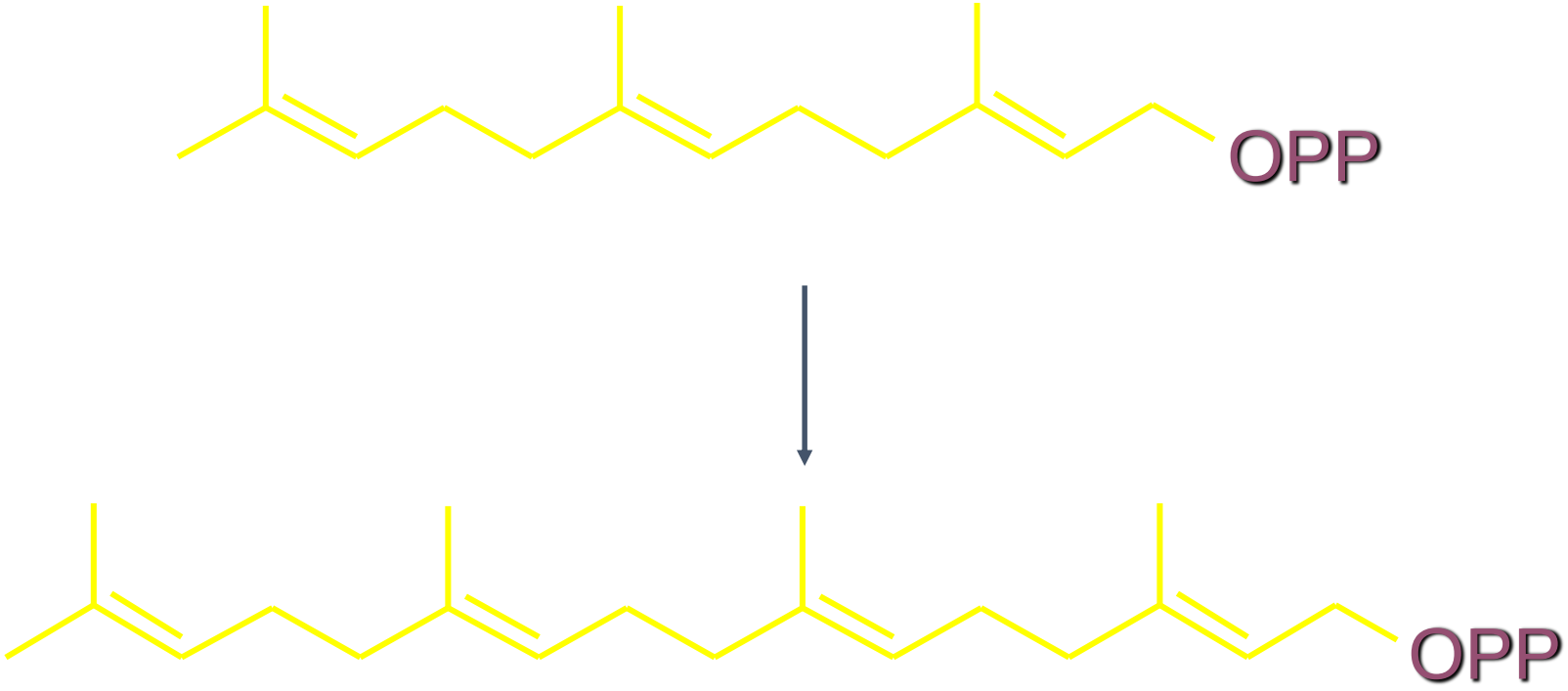
FPP + IPP = GGPP



✓precursor of C20 diterpenes

GGPP cont.

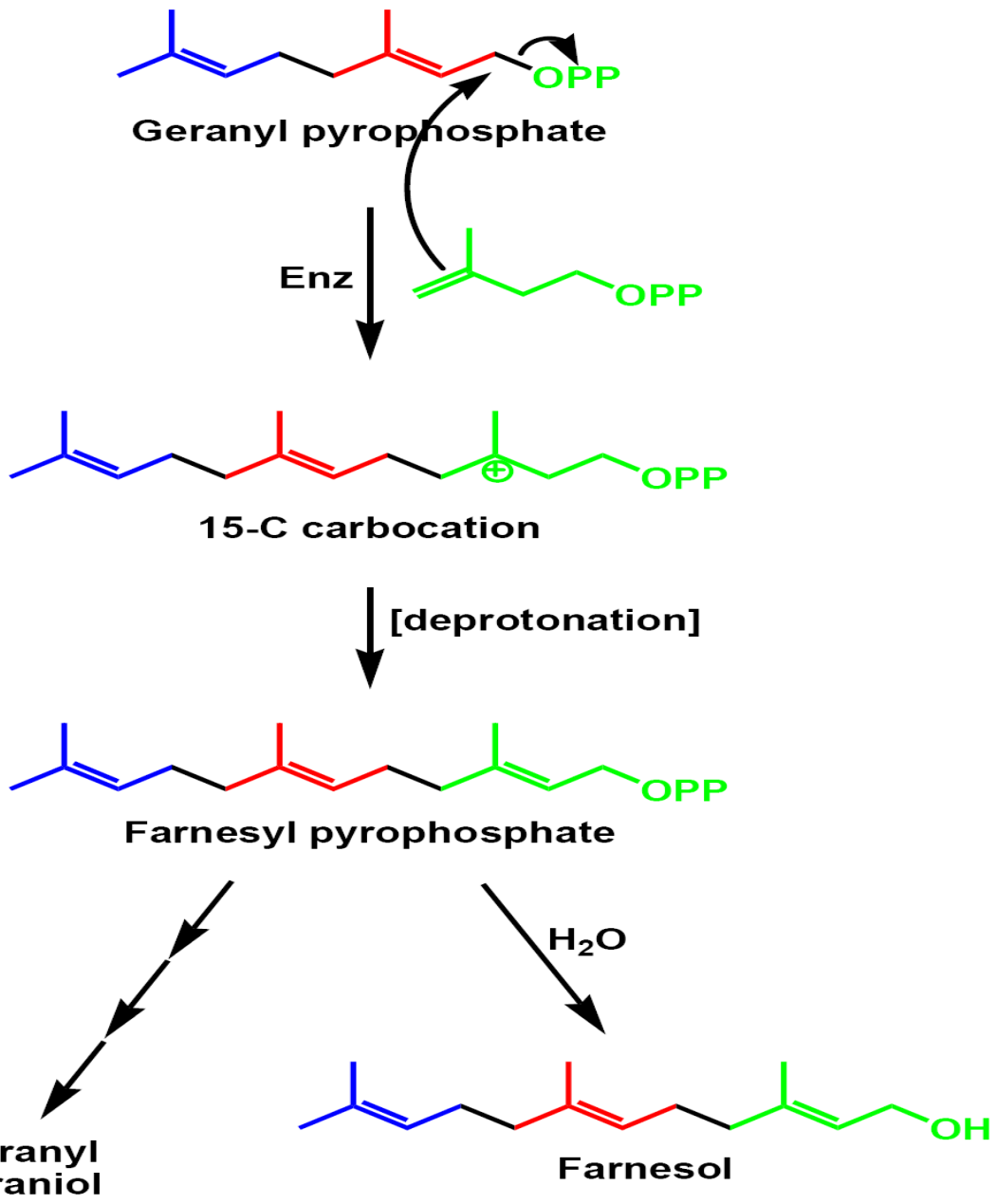
FPP is extended by another isoprene unit by reaction with IPP.

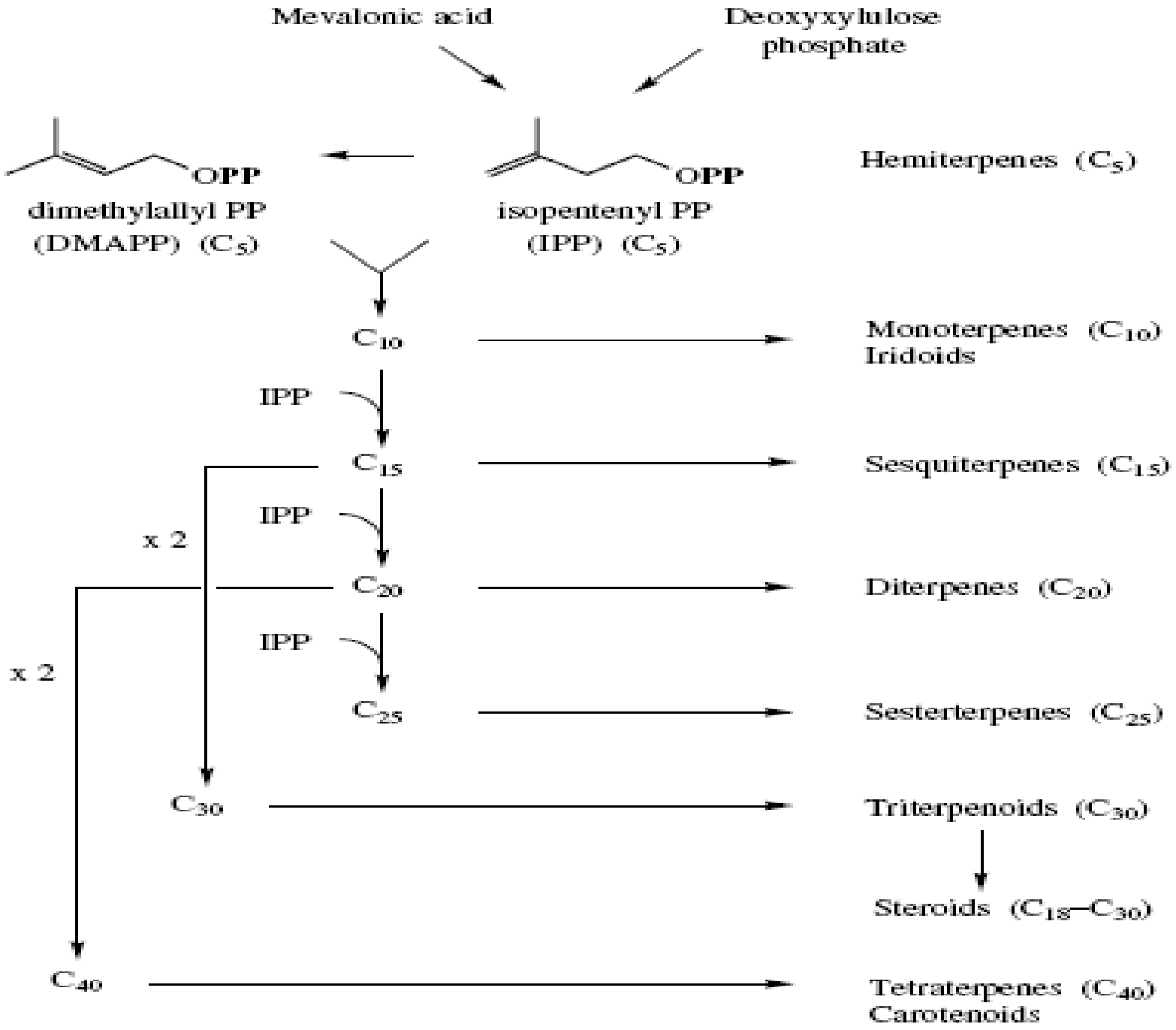


Biosynthesis of terpenoids cont.

- In similar fashions, the core pathway up to C25 compounds (five isoprene units) is formed by sequential addition of C5 moieties derived from IPP to a starter unit derived from DMAPP.
  - Thus, sesquiterpenes are formed form the precursor FPP and diterpenes from GGPP.

Biosynthesis of terpenoids cont.




Mevalonic acid
Deoxyxylulose phosphate
OPP
dimethylallyl PP (DMAPP) (C5)
OPP
isopentenyl PP (IPP) (C5)
Hemiterpenes (C5)
C10
Monoterpenes (C10) Iridoids
IPP
C15
Sesquiterpenes (C15)
IPP
x 2
C20
Diterpenes (C20)
IPP
x 2
C25
Sesterterpenes (C25)
C30
Triterpenoids (C30)
Steroids (C18—C30)
C40
Tetraterpenes (C40) Carotenoids

Biosynthesis of terpenoids cont.

- Rubbers and other polyisoprenoids are produced from repeated additions of C5 units to the starter unit GGPP

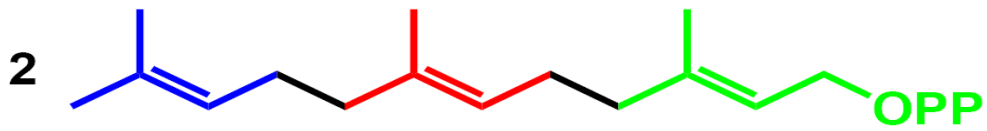
Biosynthesis of terpenoids cont.

- Higher terpenes formed from coupling of terpenes via another mechanism, not successive addition of C5 units also exist:
  - The parents of triterpenes (C30) and tetraterpenes (C40) are formed by reductive coupling of two FPPs or GGPPs, respectively.

Biosynthesis of terpenoids cont.

- **Squalene** (C30) and **phytoene** (C40), although formed entirely of isoprene units, display a tail-to-tail linkage at the centre of the molecules.
- Yet, they do not completely escape the isoprene rule
- The other C30 (indirectly steroids) and C40 families arise from sequalene and phytoene, respectively

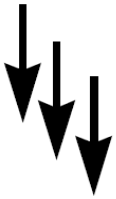
Biosynthesis of terpenoids cont.



Farnesyl pyrophosphate

Triterpene C_{30}

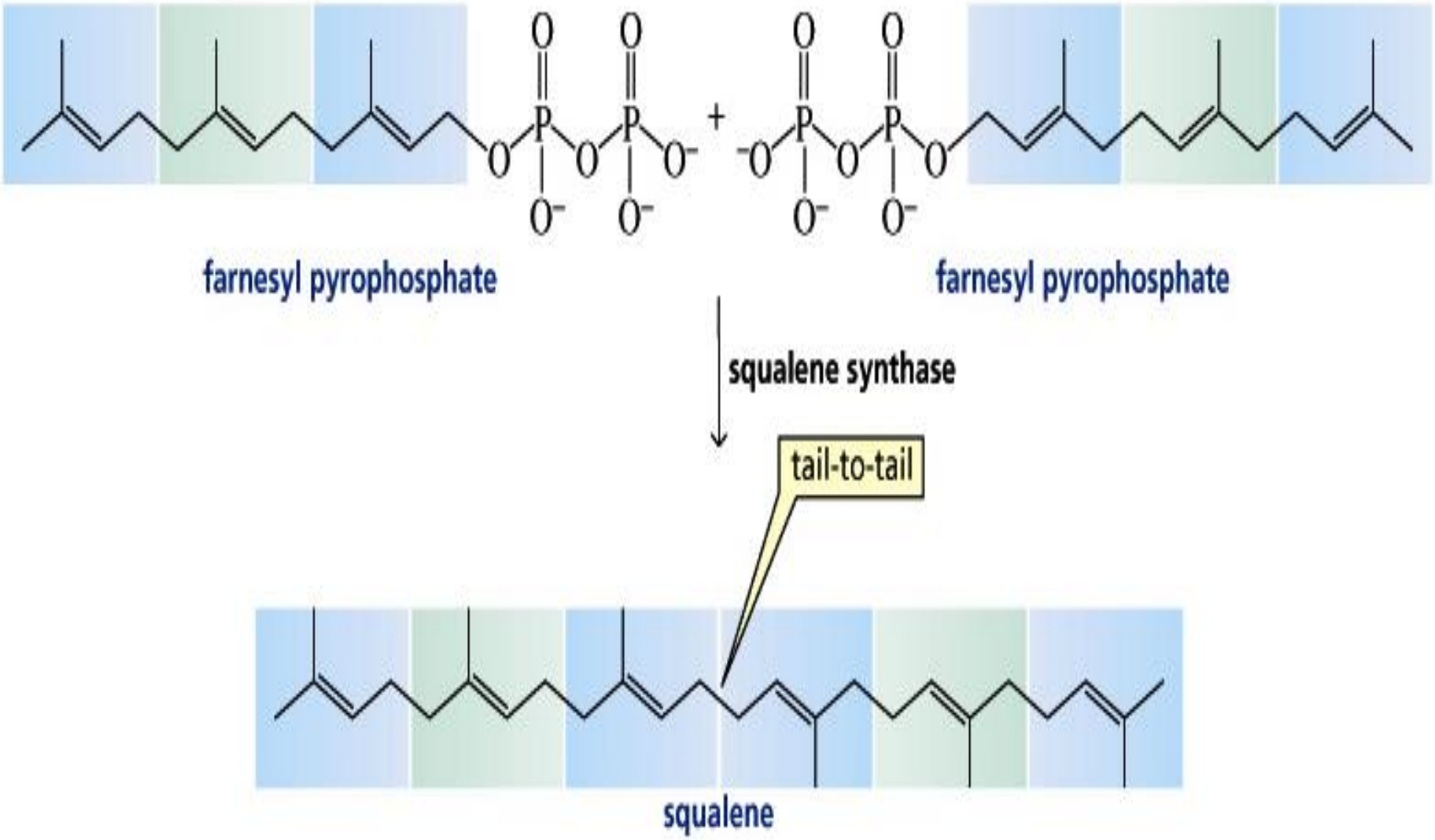
(tail to tail coupling)



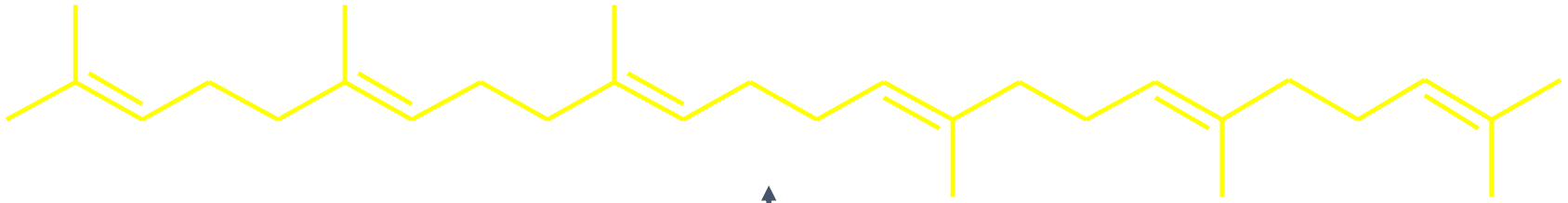
Steroids

Steroid Biosynthesis

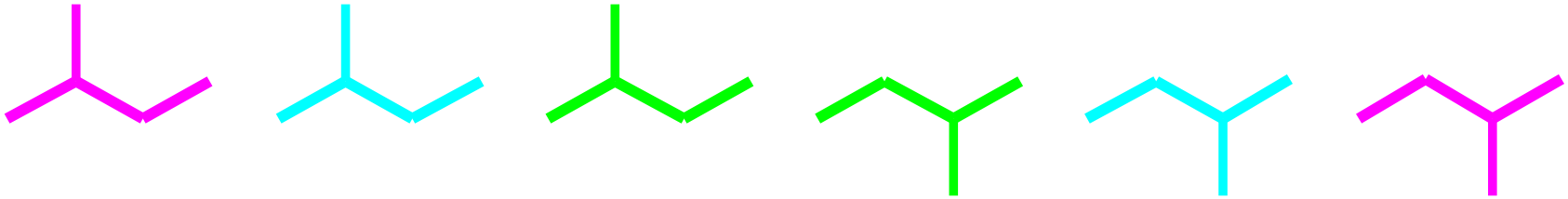
Formation of Squalene



Representative Triterpene



tail-to-tail linkage of isoprene units



Squalene (shark liver oil)

squalene

Squalene, a triterpene, is a precursor of steroids

Biosynthesis of terpenoids cont.

❖Most terpenoids are modified further by cyclization reactions, but the head-to-tail arrangement of the units can usually still be recognized, e.g. **menthol**, **bisabolene**, and **taxadiene**.

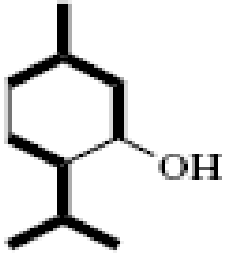
geraniol

farnesol

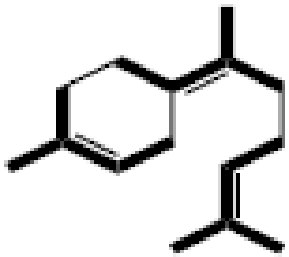
geranylgeraniol

squalene

phytoene



menthol



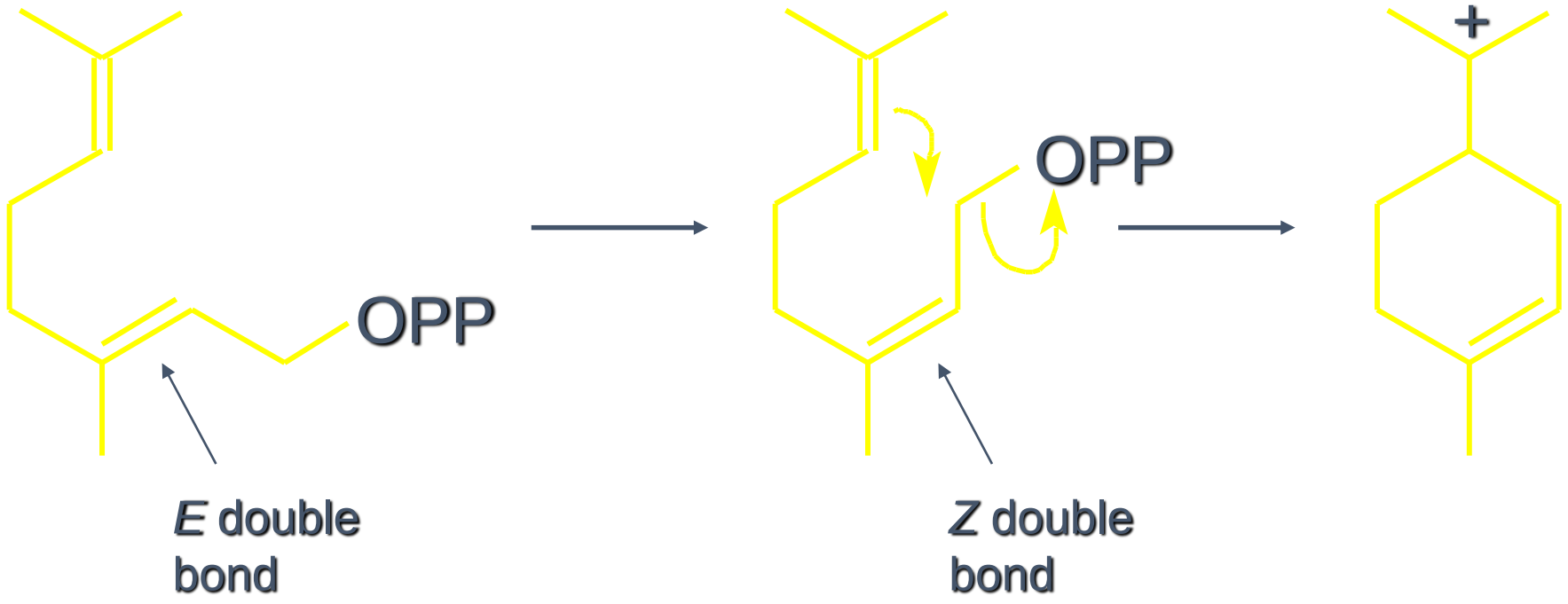
bisabolene

taxadiene

Biosynthesis of terpenoids cont.

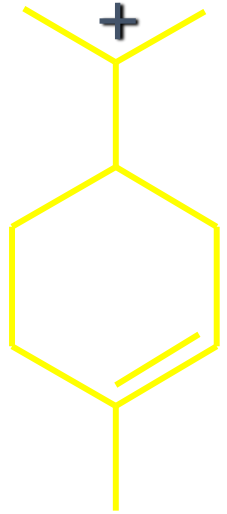
Cyclization

- Rings form by intramolecular carbon-carbon bond formation.



Limonene

$-H^+$

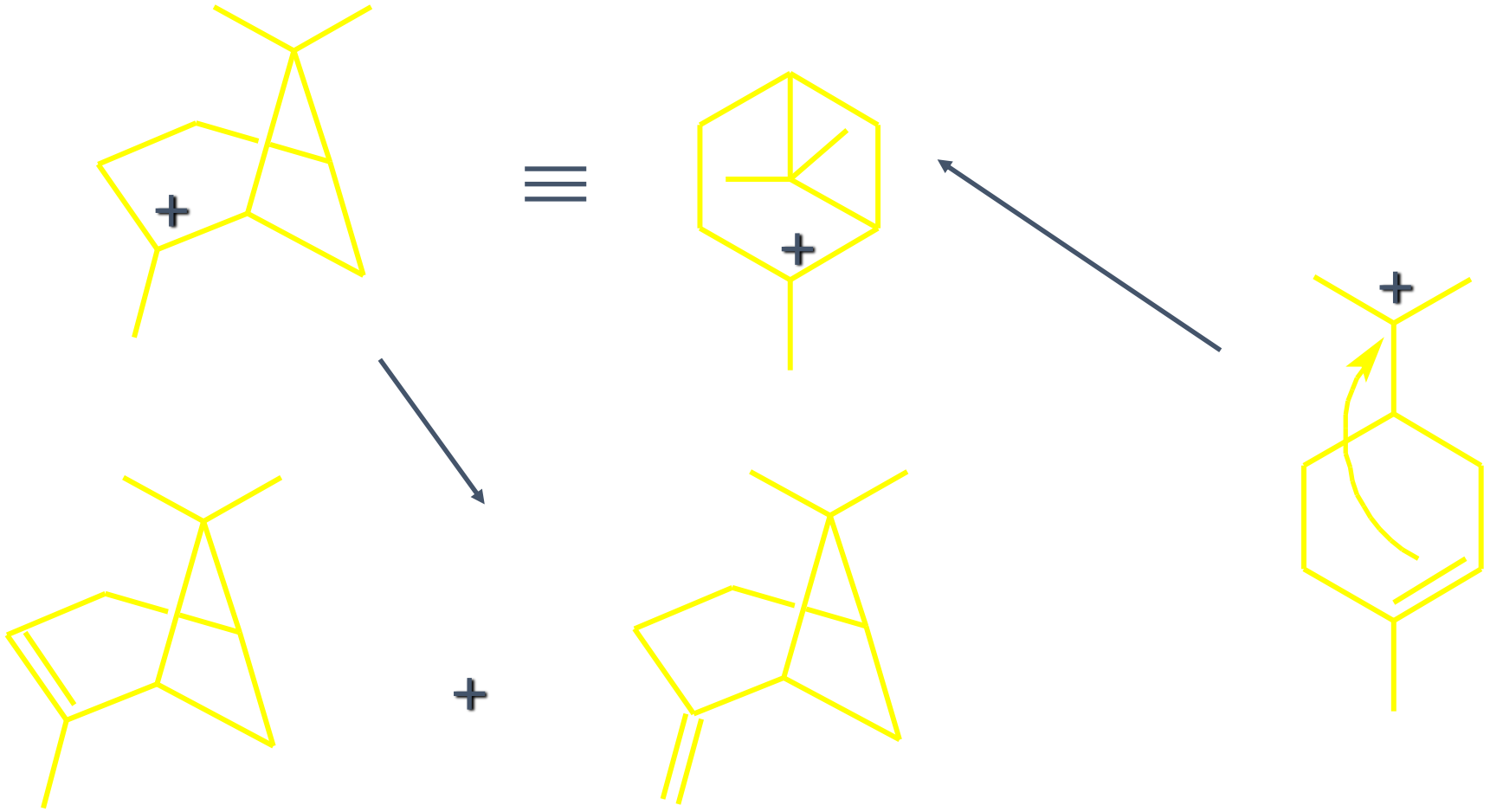


OH

H_2O

α-Terpineol

Bicyclic Terpenes



α-Pinene

β-Pinene

Biosynthesis of terpenoids cont.

- In a few cases, the isoprene rule does not seem to be followed:
  - " irregular" monoterpenes (e.g pyrethric acid, santonilatriene) arise from the coupling of two DMAPP units, by a mechanism similar to the one which leads triterpenes and carotenes

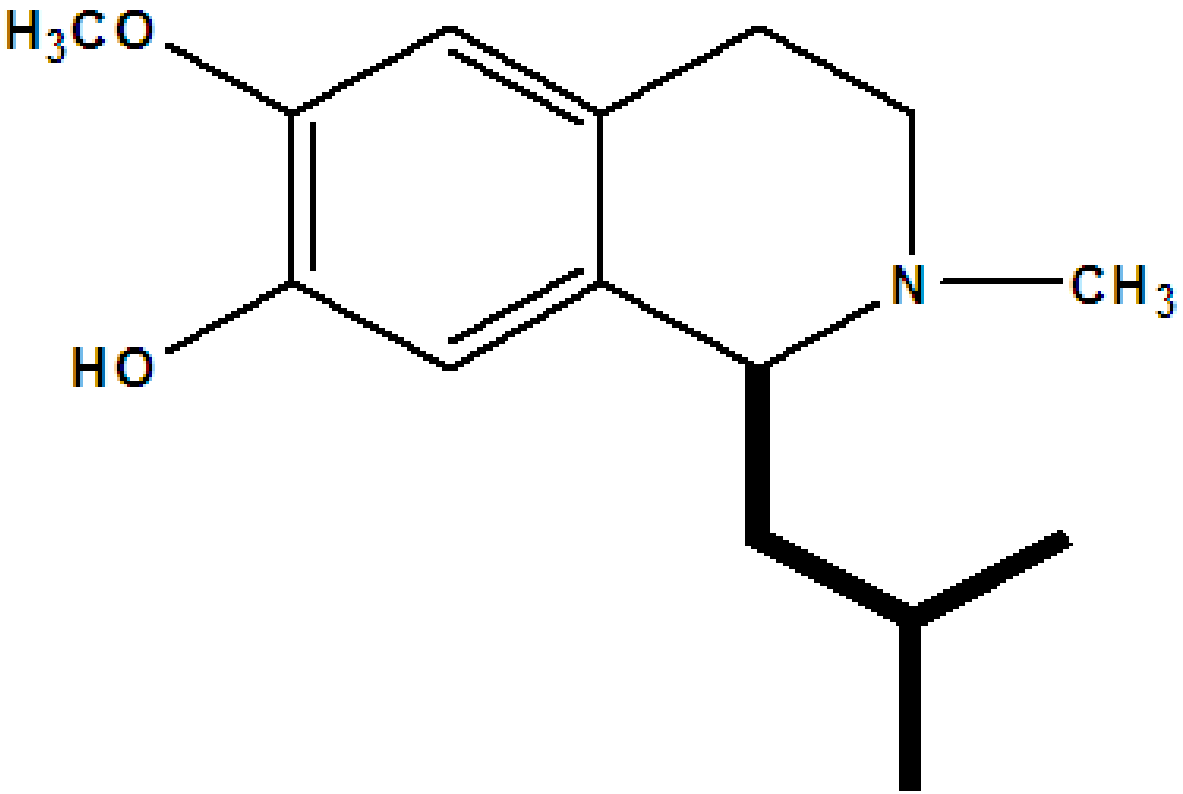
3. The different classes of terpenoids (reading assignment)

- **Hemiterpenoids (C5)**
  - Naturally occurring "hemiterpenoids" structures are rather exceptional
  - The isoprene moiety is fairly often involved in elaborating the structure of a large number of secondary metabolites of so-called mixed origin:
    - This is a result of the reactivity of DMAPP, an efficient alkylting agent.

Hemiterpenoids cont.

- This is observed among polyphenols, for example,
  - coumarins such as bergapten,
  - isoflavonoids such as rotenone, and
  - naphtoquinones such as shikonin.
- This is also the case for some alkaloids, for example,
  - the C5 unit is apparent in some Cactaceae alkaloids (e.g lophocereine)

Hemiterpenoids cont.



Lophocereine

Hemiterpenoids cont.

- it is also found in the furan and pyran ring which characterizes several quinoline derivatives from Rutaceae, and
- although at first it is not obvious, it is present in the ergoline nucleus (ergot alkaloids)

classes of terpenoids cont.

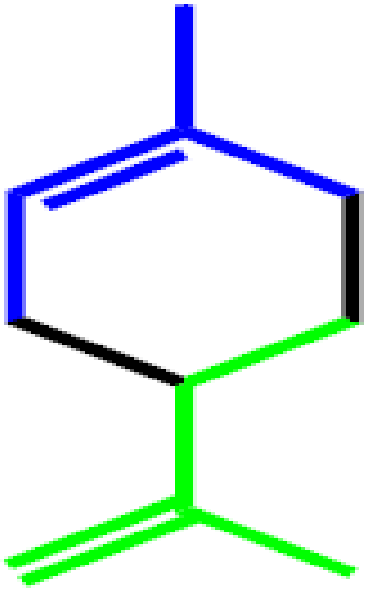
- **Monoterpenes (C10)**
  - Composed of two isoprene units,
  - GPP is the precursor of all monoterpenes.
  - Occur in plants in various **structural forms**;
    - Some are **cyclic** while the others are **acyclic**.

Monoterpenes cont.

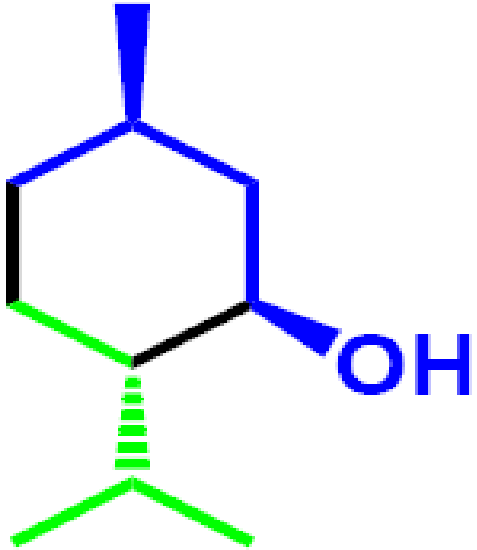
- Contain various types of **functional group**,
  - Depending on their functional groups they can be classified as
    - ✓ Simple hydrocarbons,
    - ✓ alcohols,
    - ✓ ketones,
    - ✓ aldehydes,
    - ✓ acids or phenols.

Monoterpenes cont.

- Examples include: limonene, menthol



Limonene
(from lemon or orange oil)



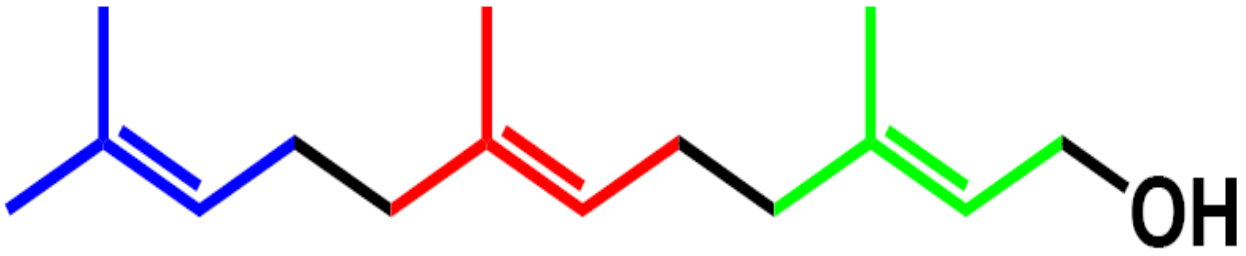
Menthol
(from peppermint)

classes of terpenoids cont.

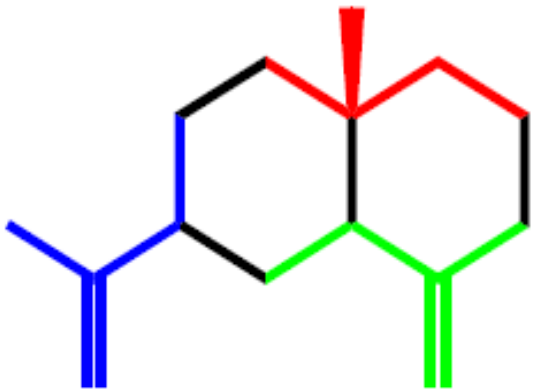
- **Sesquiterpenes (C15)**
  - Composed of three isoprene units,
  - Occur in plants in various **structural forms**;
    - Some are **cyclic** while the others are **acyclic**.
  - Contain various types of **functional group**

Sesquiterpenes cont.

- Examples include: fernasol, Selinene



Farnesol (terpenoid)



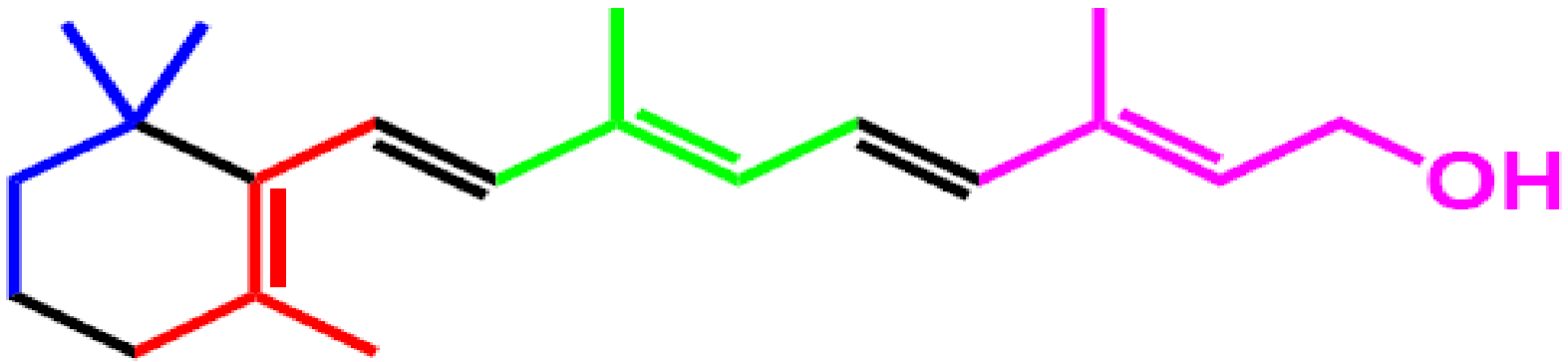
Selinene (from celery oil)

classes of terpenoids cont.

- **Diterpenes (C20)**
  - One of the simplest and most significant of the diterpenes is phytol,
  - Phytol:
    - is a reduced form of geranylgeraniol
    - constitutes the lipophilic side-chain of the chlorophylls
    - also forms a part of vitamin **E** (tocopherols) and **K** molecules.

Diterpenes cont.

- **Vitamin A** is also a 20-carbon-containing compound, and
  - can be regarded as a diterpene.
- However, vitamin A is formed from a cleavage of a tetraterpene.



Vitamin A

Diterpenes cont.

- **Major structural types**
  - While there are a number of acyclic diterpenes such as phytol, cyclization of these acyclic diterpenes, driven by various enzymes, leads to the formation of cyclic diterpenes.
  - A number of other biogenetic reactions, e.g. oxidation, also bring in variation among these cyclic diterpenes.

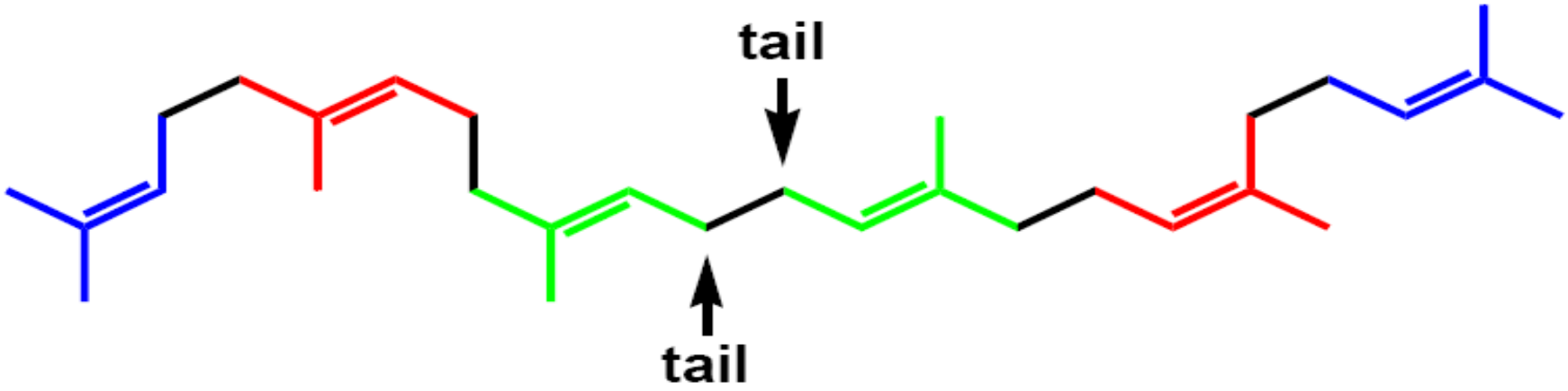
classes of terpenoids cont.

- **Triterpenes**
  - Encompass a large and diverse group of naturally occurring 30-carbon-atom-containing compounds derived from squalene
  - Two molecules of farnesyl pyrophosphate are joined tail-to-tail to yield squalene.

Triterpenes cont.

- **Major structural types**
  - –Squalene is a linear acyclic compound,
  - –Majority of triterpeneoids exist in cyclic forms
    - ➢ **penta-** and **tetracyclic** triterpenes are the major types
  - – Within these cyclic triterpenoids distinct structural variations lead to several structural classes of triterpenoids.

Triterpenes cont.



Squalene (from shark liver oil)

classes of terpenoids cont.

- **Tetraterpenoids** (C40)
  - They include carotenoids
  - Beta-carotene is the precursor of the anti-oxidant vitamin A, also called retinol.
  - Carotenoids are water insoluble plastid pigments associated with chlorophylls.

Tetraterpenoids cont.

- They are found in
  - —tomatoes,
  - —red peppers,
  - —carrots,
  - —sweet potatoes, and
  - —in many colorful flowers and autumn leaves
- Note: Some of the brilliant red pigments in autumn leaves are actually anthocyanins, a different class of chemicals called phenolic compounds

Tetraterpenoids cont.

- The bright red pigments in some algae and bacteria are carotenoids.
- In these unicellular organisms the pigments help to protect the delicate cells from intense UV light from the sun.
- Egg yolks contain **astaxanthin** which produces the characteristic yellow color.

Tetraterpenoids cont.

- Other carotenoids include
  - **zeaxanthin**, a xanthophyll pigment responsible for the yellow color of corn kernels (***Zea mays***).
- Ripe tomatoes are particularly rich in the carotenoid **lycopene**.

Tetraterpenoids cont.

- Lycopene
  - ✓Impart bright red color to tomatoes,
  - ✓40 mg ingested daily may reduce the risk of
    - atherosclerosis and heart disease
  - ✓may also reduce the risk of certain cancers, including cancers of the prostate, lung, bladder, cervix, skin and digestive tract.

classes of terpenoids cont.

- **Polyterpenes** (>C40)
- Elastic terpenes composed of thousands of C_5H_8 isoprene subunits
- They are found in the milky latex sap produced inside special cells called laticifers or laticiferous tubules in the secondary phloem.

Polyterpenes cont.

- A process called vulcanization produces cross-linkages between the thousands of isoprene subunits in the rubber latex, improving the elasticity and durability of the rubber.

4. Properties and isolation of terpenoids

•4.1 General properties of Terpenoids

–Most are

- ✓colourless,
- ✓fragrant liquids which are lighter than water and
- ✓volatile with steam.

–A few of them are solids e.g. camphor.

–All are soluble in organic solvent and usually insoluble in water.

–Most of them are optically active.

Properties and isolation cont.

–They are open chain or cyclic unsaturated compounds having one or more double bonds.

- ✓Consequently they undergo addition reaction with hydrogen, halogen, acids, etc.
- ✓A number of addition products have antiseptic properties.

Properties and isolation cont.

- They undergo polymerization and dehydrogenation
- They are easily oxidized nearly by all the oxidizing agents.
- On thermal decomposition, most of the terpenoids yields isoprene as one of the products.

Properties and isolation cont.

- **4.2 Extraction and isolation of terpenoids**
  - –Terpenes are isolated from essential oils or solvent extracts
  - –The simpler mono and sesqui terpenes are chief constituent of essential oils.
    - ✓They occur in leaves, flowers and fruits, often imparting a distinctive odor and flavor

Properties and isolation cont.

–The di and tri terpenoids are not steam volatile.

✓They are obtained from plants and plant exudates such as resins and gum-resins.

–Tertraterpenoids form a separate group of compounds called 'Carotenoids'

Properties and isolation cont.

- **Extraction**
- There are four methods of extractions of oils.
    a) Expression
    b) Steam distillation
    c) Extraction by means of volatile solvents
    d) Adsorption in purified fats
- Steam distillation is most widely used method.
- None polar solvents are used to extract terpenes from plants and plant exudates

Properties and isolation cont.

- **Separation and isolation of terpenoids from essential oils**
- From essential oils:
  - A number of terpenoids are present in essential oils
  - Definite physical and chemical methods can be used for the separation of terpenoids.
  - They are separated by fractional distillation.

Properties and isolation cont.

- The terpenoid hydrocarbons distill over first followed by the oxygenated derivatives.
- More recently different chromatographic techniques have been used both for isolation and separation of terpenoids.

5. Significance of terpenoids

- **Society and terpenes**
  - There have been many applications of terpenes in human societies and possibly, society has benefited tremendously from terpenes.
  - Perhaps the most widely known terpene is rubber, which has been used extensively by humans.
    - Rubber is a polyterpene, composed of repeating subunits of isoprene.

Significance cont.

- ✓Of course, some terpenes are poisonous.
  - –Excellent examples of these terpenes can be found in the milky sap of some members of the euphorbia family (Euphorbiaceae).

Significance cont.

- Pharmaceutical and food industries have exploited terpenoids for their potentials and effectiveness as **medicines** and **flavor enhancers**.
- Terpenoids are incorporated into antibacterial soaps, cosmetics and household products
- Generally terpenoids are used as:
  - ✓Insecticides, Fragrances and Perfumes, Food Additives, Aroma therapy, Cleaning Products (Pinesol) and Medicines